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L4 ANSWER 1 OF 17 MEDLINE on STN DUPLICATE 1
2005436139. PubMed ID: 16102449. Effect of short-term **treatment** with pravastatin on cytokines and cytokine receptors in patients with **chronic heart failure** due to ischemic and nonischemic disease. Conraads Viviane M; Bosmans Johan M; Schuerwegh Annemie J; De Clerck Luc S; Bridts Chris H; Wuyts Floris L; Stevens Wim J; Vrints Christiaan J. (Department of Cardiology, University Hospital, Antwerp, Belgium.) Journal of heart and lung transplantation : official publication of the International Society for Heart Transplantation, (2005 Aug) 24 (8) 1114-7. Journal code: 9102703. ISSN: 1053-2498. Pub. country: United States. Language: English.

AB The antiinflammatory effect of lipoproteins through neutralization of circulating **endotoxin** has questioned the safety of lipid-lowering drugs in **chronic heart failure** (CHF). We measured serum levels of interleukin-6, tumor necrosis factor (TNF)-alpha, and soluble TNF-alpha receptors 1 and 2 before and after 1-month **treatment** with pravastatin 40 mg in 58 patients with CHF. Short-term **treatment** with pravastatin attenuated the immune response in patients with CHF due to ischemic or nonischemic etiology.

L4 ANSWER 2 OF 17 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

2005137145 EMBASE Future prospects of anticytokine therapy in **chronic heart failure**. von Haehling S.; Anker S.D.. Dr. S. von Haehling, Imperial Coll. School of Medicine, Department of Clinical Cardiology, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, United Kingdom. stephan.von.haehling@web.de. Expert Opinion on Investigational Drugs Vol. 14, No. 2, pp. 163-176 2005.
Refs: 108.
ISSN: 1354-3784. CODEN: EOIDER
Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20050414

AB Several lines of evidence suggest that **chronic heart failure** is a state of chronic inflammation. Indeed, various pro-inflammatory markers, including the cytokines TNF-α, and interleukin 6 and 1, are activated in the course of the disease. In **chronic heart failure**, these substances are frequently induced even before the classical neurohormones angiotensin II and noradrenaline. Although the recently published anti-TNF-α trials with etanercept and infliximab have called the beneficial effects of targeting single cytokines into question, the overactive immune system remains a promising target for therapeutic interventions, which aim at slowing down disease progression. Broader approaches are required. These comprise targeting bacterial lipopolysaccharide (**endotoxin**) that enters the circulation through the oedematous gut wall, immune modulation therapy with patient-derived whole blood exposed to oxidative stress, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (the so-called statins) and a number of other substances including pentoxifylline and thalidomide. .COPYRGT. 2005 Ashley Publications Ltd.

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2004172529 EMBASE Reverse epidemiology of conventional cardiovascular risk factors in patients with **chronic heart failure**. Kalantar-Zadeh K.; Block G.; Horwich T.; Fonarow G.C.. Dr. G.C. Fonarow, Ahmanson-UCLA Cardiomyopathy Center, Division of Cardiology, Univ. of California at Los Angeles, 10833 LaConte Avenue, Los Angeles, CA 90095-1679, United States. gfonarow@mednet.ucla.edu. Journal of the American College of Cardiology Vol. 43, No. 8, pp. 1439-1444 21 Apr 2004.
Refs: 62.
ISSN: 0735-1097. CODEN: JACCDI
S 0735-1097(04)00172-X. Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20040513

AB Traditional risk factors of a poor clinical outcome and mortality in the general population, including body mass index (BMI), serum cholesterol, and blood pressure (BP), are also found to relate to outcome in patients with **chronic heart failure** (CHF), but in an opposite direction. Obesity, hypercholesterolemia, and high values of BP have been demonstrated to be associated with greater survival among CHF patients. These findings are in contrast to the well-known associations of over-nutrition, hypercholesterolemia, and hypertension with a poor outcome in the general population. The association between traditional cardiovascular risk factors and an adverse clinical outcome in CHF patients is referred to as "reverse epidemiology." The mechanisms for this inverse association in CHF is not clear. There are other populations with a similar risk factor reversal phenomenon, including patients with end-stage renal disease receiving dialysis, those with advanced malignancies, and individuals with advanced age. Several possible causes are hypothesized: the time discrepancy of the competing risk factors may play a role; the presence of the "malnutrition-inflammation complex syndrome" in CHF patients may explain the existence of reverse epidemiology; and a decreased level of lipoprotein molecules may distort

their **endotoxin**-scavenging role, predisposing CHF patients with a low serum cholesterol level to inflammatory consequences of endotoxemia. It is possible that new goals for such traditional risk factors as BMI, serum cholesterol, and BP should be developed for CHF. Reverse epidemiology of conventional cardiovascular risk factors is observed in CHF and may have a bearing on the management of these patients; thus, it deserves further investigation. .COPYRGT. 2004 by the American College of Cardiology Foundation.

L4 ANSWER 4 OF 17 MEDLINE on STN DUPLICATE 2

2004283437. PubMed ID: 15182775. Selective intestinal decontamination in advanced **chronic heart failure**: a pilot trial. Conraads Viviane M; Jorens Philippe G; De Clerck Luc S; Van Saene Hendrik K; Ieven Margaretha M; Bosmans Johan M; Schuerwegh Annemie; Bridts Chris H; Wuyts Floris; Stevens Wim J; Anker Stefan D; Rauchhaus Mathias; Vrints Christiaan J. (Department of Cardiology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium.. Viviane.Conraads@uza.be) . European journal of heart failure : journal of the Working Group on Heart Failure of the European Society of Cardiology, (2004 Jun) 6 (4) 483-91. Journal code: 100887595. ISSN: 1388-9842. Pub. country: Netherlands. Language: English.

AB BACKGROUND AND AIMS: **Endotoxin**, derived from intestinal aerobic Gram-negative bacilli (AGNB), could be an important monocyte activator in **chronic heart failure** (CHF). The effect of selective decontamination of the digestive tract (SDD) on intracellular monocyte cytokine production, monocyte CD14 expression, circulating **endotoxin** and cytokines, and flow-mediated dilation (FMD) was studied in patients with severe CHF. METHODS AND RESULTS: Ten patients with CHF (NYHA class III-IV) were enrolled in a non-placebo controlled pilot trial involving the administration of SDD (polymyxin B, tobramycin) for 8 weeks. One patient was later excluded due to cardiac transplantation. Before **treatment**, after 4 and 8 weeks therapy, and 6 weeks post-**treatment**, monocyte CD14 expression, intracellular monocyte production of interleukin-1beta [IL-1beta], interleukin-6 [IL-6], tumour necrosis factor (TNF)-alpha with and without lipopolysaccharide (LPS) stimulation were measured. Concentrations of **endotoxin** and cytokines (IL-1beta, IL-6, TNF-alpha) were also determined. AGNB in faeces, intestinal **endotoxin** and FMD were assessed at baseline, after 4 weeks of **treatment** and 6 weeks post-**treatment.** SDD eradicated intestinal AGNB (P<0.00001) and decreased faecal **endotoxin** concentrations (P<0.00001). There was a significant decline in monocyte CD14 expression (P=0.03) and in IL-1beta (P=0.0001), IL-6 (P=0.02) and TNF-alpha (P=0.0002) production after 4 and 8 weeks of **treatment** in the basal state and for IL-1beta (P=0.008) and IL-6 (P=0.005) after LPS stimulation. FMD significantly improved at 4 weeks and returned to baseline after **treatment** discontinuation (P=0.002). Circulating concentrations of **endotoxin** and cytokines remained unchanged. CONCLUSION: Reduction of the intestinal **endotoxin** pool led to a decrease in monocyte CD14 expression and intracellular cytokine production in patients with severe CHF. The improvement of peripheral endothelial function could be a marker of the anti-inflammatory effect of SDD.

L4 ANSWER 5 OF 17 MEDLINE on STN DUPLICATE 3

2005139950. PubMed ID: 15772704. Statins: a **treatment** option for **chronic heart failure**?. Haehling Stephan von; Okonko Darlington O; Anker Stefan D. (National Heart and Lung Institute, Department of Clinical Cardiology, Imperial College School of Medicine, London, UK, and Division of Applied Cachexia Research, Department of Cardiology, Charite Medical School, Berlin, Germany.) Heart failure monitor, (2004) 4 (3) 90-7. Journal code: 101140283. ISSN: 1470-8590. Pub. country: England: United Kingdom. Language: English.

AB Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, consistently reduce cardiovascular risk. It has recently emerged that cholesterol reduction is not their only mode of

action, with current research largely focused on the pleiotropic effects of statins. These include the improvement of endothelial dysfunction, their anti-inflammatory properties, and the mobilization of bone marrow-derived endothelial progenitor cells. All these effects are potentially beneficial in **chronic heart failure** (CHF), although prospective trials are needed to confirm this. However, cholesterol reduction by statins per se may prove detrimental in patients with CHF, as cholesterol seems to be able to inactivate **endotoxin** as a stimulus for proinflammatory cytokine production. It is therefore tempting to speculate that low doses of statins still confer pleiotropic effects without lowering plasma cholesterol levels.

L4 ANSWER 6 OF 17 MEDLINE on STN DUPLICATE 4

2003529563. PubMed ID: 14607199. Invasive assessment of bacterial **endotoxin** and inflammatory cytokines in patients with acute heart failure. Peschel Thomas; Schonauer Martin; Thiele Holger; Anker Stefan D; Schuler Gerhard; Niebauer Josef. (Herzzentrum der Universitat Leipzig, Strumpellstrasse 39, 04289 Leipzig, Germany.) European journal of heart failure : journal of the Working Group on Heart Failure of the European Society of Cardiology, (2003 Oct) 5 (5) 609-14. Journal code: 100887595. ISSN: 1388-9842. Pub. country: Netherlands. Language: English.

AB AIMS: To test the hypothesis that during acute heart failure **endotoxin** might be increased in hepatic veins as a sign of bacterial or **endotoxin** translocation from the bowel into the blood stream. METHODS AND RESULTS: In patients with acute heart failure (NYHA IV; n=17) levels of **endotoxin**, soluble (s) CD14, tumor necrosis factor alpha (TNFalpha and interleukin 6 (IL6)) were measured in blood drawn from an antecubital vein on admission and compared with age-matched patients with stable **chronic heart failure** (n=21) and healthy volunteers (n=9). All levels were systemically elevated during acute heart failure (all P<0.05); once patients were stable enough to undergo cardiac catheterization, **endotoxin** was found to be significantly higher in hepatic veins (0.62+/-0.05 EU/ml) than left ventricles (0.46+/-0.04 EU/ml; P<0.05), whereas sCD14, TNFalpha and IL6 were not different between these sites. At follow-up (29+/-6 days) **endotoxin** but not sCD14, TNFalpha or IL-6 was significantly lower as compared to baseline (P<0.05). CONCLUSIONS: Higher levels of **endotoxin** in hepatic veins as compared to the left ventricle during acute heart failure are suggestive of bacterial or **endotoxin** translocation from the bowel into the blood stream. This may lead to new **treatment** strategies. The lack of difference in TNFalpha levels between the pulmonary artery and the left ventricle sheds doubt on the heart as a source of systemically elevated TNFalpha levels.

L4 ANSWER 7 OF 17 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2003:690892 The Genuine Article (R) Number: 708KA. Therapeutic effects of ghrelin on endotoxic shock in rats. Chang L; Zhao J; Yang J; Zhang Z K; Du J B; Tang C S (Reprint). Peking Univ, Hosp 1, Cardiovasc Res Inst, Beijing 100034, Peoples R China (Reprint); Peking Univ, Ctr Hlth, Dept Physiol & Pathophysiol, Beijing 100083, Peoples R China; Phoenix Pharmacert Inc, Belmont, CA 94002 USA; Peking Univ, Hosp 1, Dept Pediat, Beijing 100034, Peoples R China. EUROPEAN JOURNAL OF PHARMACOLOGY (25 JUL 2003) Vol. 473, No. 2-3, pp. 171-176. ISSN: 0014-2999. Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB We investigated the effects of ghrelin in a rat endotoxic shock model, and also observed the direct role of **endotoxin** on ghrelin generation in gastric mucosa. About 55% (11/20) of rats treated with lipopolysaccharide (5 mg/kg i.v.) alone died within 24 h of **endotoxin** injection. However, administration of ghrelin either at the same time as lipopolysaccharide injection (early **treatment**) or 12 h after lipopolysaccharide injection (late **treatment**)

significantly decreased the mortality rate and ameliorated the hypotension seen in rats with endotoxic shock. Early and late **treatment** with ghrelin increased markedly the plasma glucose concentration and decreased the plasma lactate concentration. Early **treatment** with ghrelin attenuated significantly the deficiency in myocardial ATP content, but late **treatment** with ghrelin had no effect on myocardial ATP content. The plasma ghrelin level was significantly increased in the rats with **endotoxin** shock, and it increased further after ghrelin administration: Exposure of rat gastric mucosa in vitro to lipopolysaccharide (1.0 to 100 mug/ml) triggered the release of ghrelin from mucosa tissue in a dose- and time-dependent manner, meaning that lipopolysaccharide stimulated directly gastric mucosa to synthesize and secrete ghrelin. The results suggest that ghrelin could have therapeutic value for endotoxic shock.

L4 ANSWER 8 OF 17 EMBASE

2002169891 EMBASE Statins and **chronic heart failure**: Do we need a large-scale outcome trial?. Krum H.; McMurray J.J.. Prof. H. Krum, Department of Epidemiology, Monash University, Alfred Hospital, Prahran, Vic. 3181, Australia. henry.krum@med.monash.edu.au. Journal of the American College of Cardiology Vol. 39, No. 10, pp. 1567-1573 15 May 2002.
Refs: 56.
ISSN: 0735-1097. CODEN: JACCDI
S 0735-1097(02)01827-2. Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20020523

AB Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) are of proven clinical benefit in coronary heart disease, at least in those patients who do not have overt **chronic heart failure** (CHF). However, as there have been no prospective clinical trials of statins in CHF patients, the question arises as to whether the benefits observed in the absence of CHF can be necessarily inferred in those patients in whom CHF is established. In this review, the evidence base stating support of the use of statins in CHF is presented, as well as theoretical considerations as to why these agents may not necessarily be of benefit in this setting. The beneficial potential of statins clearly relates to their plaque stabilization properties and associated improvements in endothelial function, which together should reduce the risk of further infarction and, perhaps, the ischemic burden on the failing ventricle. Furthermore, these agents may have beneficial effects independent of lipid lowering. These include actions on neoangiogenesis, downregulation of AT(1) receptors, inhibition of proinflammatory cytokine activity and favorable modulation of the autonomic nervous system. The potential adverse effects of statins in CHF include reduction in levels of coenzyme Q10 (which may further exacerbate oxidative stress in CHF) and loss of the protection that lipoproteins may provide through binding and detoxifying **endotoxins** entering the circulation via the gut. In support of these possibilities are epidemiologic data linking a lower serum cholesterol with a poorer prognosis in CHF. These uncertainties indicate the need for a definitive outcome trial to assess the efficacy and safety of statins in CHF, despite their current widespread, nonevidence based use in this population.

L4 ANSWER 9 OF 17 SCISEARCH

2002:924577 The Genuine Article (R) Number: 613AY. The therapeutic potential of endothelin-1 receptor antagonists and endothelin-converting enzyme inhibitors on the cardiovascular system. Doggrell S A (Reprint). Univ Queensland, Sch Biomed Sci, Dept Physiol & Pharmacol, St Lucia, Qld 4072, Australia (Reprint). EXPERT OPINION ON INVESTIGATIONAL DRUGS (NOV 2002) Vol. 11, No. 11, pp. 1537-1552. ISSN: 1354-3784. Publisher: ASHLEY

PUBLICATIONS LTD, UNITEC HOUSE, 3RD FL, 2 ALBERT PLACE, FINCHLEY CENTRAL, LONDON N3 1QB, ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Clinical trials have established bosentan, an orally active non-selective endothelin (ET) receptor antagonist, as a beneficial **treatment** in pulmonary hypertension. Trials have also shown short-term benefits of bosentan in systemic hypertension and congestive heart failure. However, bosentan also increased plasma levels of ET-1, probably by inhibiting the clearance of ET-1 by endothelin type B (ET.) receptors, and this may mean its effectiveness is reduced with long-term clinical use. Preliminary data suggests that selective endothelin type A (ETA) receptor antagonists (BQ-123, sitaxsentan) may be more beneficial than the non-selective ET receptor antagonists in heart failure, especially when the failure is associated with pulmonary hypertension. Experimental evidence in animal disease models suggests that non-selective ET or selective ETA receptor antagonism may have a role in the **treatment** of athero-sclerosis, restenosis, myocarditis, shock and portal hypertension. In animal models of myocardial infarction and/or reperfusion injury, non-selective ET or selective ETA receptor antagonists have beneficial or detrimental effects depending on the conditions and agents used. Thus clinical trials of the nonselective ET or selective ETA receptor antagonists in these conditions are not presently warranted. Several selective endothelin-converting enzyme inhibitors tors have been synthesised recently, and these are only beginning to be tested in animal models of cardiovascular disease, and thus the clinical potential of these inhibitors is still to be defined.

L4 ANSWER 10 OF 17 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

2002294975 EMBASE Effect of interleukin-10 on the production of tumor necrosis factor-alpha by peripheral blood mononuclear cells from patients with **chronic heart failure.** Bolger A.P.; Sharma R.; Von Haehling S.; Doehner W.; Oliver B.; Rauchhaus M.; Coats A.J.S.; Adcock I.M.; Anker S.D.. A.P. Bolger, Department of Clinical Cardiology, National Heart and Lung Institute, London SW3 6LY, United Kingdom. a.bolger@ic.ac.uk. American Journal of Cardiology Vol. 90, No. 4, pp. 384-389 15 Aug 2002.
Refs: 29.
ISSN: 0002-9149. CODEN: AJCDAG
S 0002-9149(02)02494-3. Pub. Country: United States. Language: English.
Summary Language: English.

ED Entered STN: 20020829

AB **Chronic heart failure** (HF) is a state of inflammatory immune activation characterized by elevated circulating levels of tumor necrosis factor-α (TNF-α). Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that inhibits TNF-α production and lessens **endotoxin** bioactivity. It is not known whether IL-10 reduces lipopolysaccharide (LPS) stimulated TNF-α production of peripheral blood mononuclear cells (PBMCs) from patients with chronic HF. PBMCs were isolated from 15 patients with chronic HF (New York Heart Association functional class 3.0 ± 0.2, left ventricular ejection fraction 30 ± 2%, peak oxygen consumption 18.1 ± 0.8 ml/kg/min) and 15 healthy control subjects and stimulated with 1 and 10 ng/ml LPS for 24 hours with or without prior addition of IL-10 (10 ng/ml). TNF-α was quantified in cell-free supernatants by an enzyme-linked immunosorbent assay. TNF-α, soluble TNF receptors, IL-10, and LPS were quantified in plasma. LPS stimulated TNF-α production was highest in those patients in New York Heart Association class II ($p < 0.01$ vs New York Heart Association class III and IV, $p < 0.001$ vs control subjects). IL-10 reduced PBMC TNF-α production in all stimulated samples at 1 and 10 ng/ml LPS (mean reduction 43% at 1 ng/ml, $p < 0.01$ and 55% at 10 ng/ml, $p < 0.0001$). The percentage reduction in TNF-α release did not differ significantly between patients and control subjects or with respect to severity of chronic HF or baseline immune parameters. Independently of clinical severity, IL-10 profoundly

inhibits TNF-α release from PBMCs isolated from patients with chronic HF. IL-10 is, therefore, a potential therapy for use in chronic HF associated with inflammatory immune activation. .COPYRGT. 2002 by Excerpta Medica, Inc.

L4 ANSWER 11 OF 17 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2001:815447 The Genuine Article (R) Number: 477VG. **Endotoxin** and cytokines alter contractile protein expression in cardiac myocytes in vivo . Patten M (Reprint); Kramer E; Bunemann J; Wenck C; Thoenes M; Wieland T; Long C. Univ Hamburg, Krankenhaus Eppendorf, Abt Kardiol, Med Klin, Martinistr 52, D-20246 Hamburg, Germany (Reprint); Univ Hamburg, Krankenhaus Eppendorf, Abt Kardiol, Med Klin, D-20246 Hamburg, Germany; Univ Hamburg, Krankenhaus Eppendorf, Inst Klin & Expt Pharmakol, D-20246 Hamburg, Germany; Denver Hlth Med Ctr, Dept Cardiol, Denver, CO 80204 USA. PFLUGERS ARCHIV-EUROPEAN JOURNAL OF PHYSIOLOGY (SEP 2001) Vol. 442, No. 6, pp. 920-927. ISSN: 0031-6768. Publisher: SPRINGER-VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Release of bacterial **endotoxin** and cytokines induce cardiac failure during sepsis. We investigated the direct effects of E. coli **endotoxin** (lipopolysaccharide, LPS) and cytokines induced by LPS on the cardiac myocyte gene program. For in vivo-experiments adult Wistar rats were given 600 mug/day LPS i.v. for 24 h or 7 days. In addition. cultured adult rat cardiac myocytes were treated with LPS, interleukin-1 beta (IL-1 beta), tumour necrosis factor-alpha (TNF alpha), interferon-gamma (IFN gamma) or IL-6 for 24 h. mRNA expression was evaluated for cardiac-alpha -actin (cAct), skeletal-alpha -actin (skAct), beta- and alpha -myosin heavy chain (MHC). LPS induced beta MHC-mRNA 3.6-fold and repressed alpha MHC 2.7-fold and cAct 2.5-fold after 24 h in vivo. Up-regulation of beta MHC (3-fold) and repression of cAct (2.5-fold) were still observed after 7 days LPS infusion. whereas alpha MHC-mRNA levels had returned to normal. At the protein level. increased expression of beta MHC by LPS **treatment** occurred already after 24 h and was maintained thereafter. LPS had no influence on skAct-mRNA. Similar changes in contractile protein mRNA expression were observed in LPS-treated cardiomyocytes in culture, whereas the tested cytokines either activated (IL-1 beta, IFN gamma) or repressed (TNF alpha, IL-6) both MHC-isoforms and cAct. In conclusion. LPS and proinflammatory cytokines induce changes in contractile protein expression that may contribute to the acute heart failure observed during endotoxaemia.

L4 ANSWER 12 OF 17 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2002:16314 The Genuine Article (R) Number: 505VQ. Endovascular stent-graft placement versus conventional open surgery in infrarenal aortic aneurysm: a prospective study on acute phase response and clinical outcome. Bolke E (Reprint); Jehle P M; Storck M; Braun C; Schams S; Steinbach G; Orth K; Gorich J; Scharrer-Pamler R; Sunder-Plassmann L. Univ Ulm, Dept Thorac & Vasc Surg, Steinhovelstr 9, D-89075 Ulm, Germany (Reprint); Univ Ulm, Dept Thorac & Vasc Surg, D-89075 Ulm, Germany; Univ Ulm, Dept Internal Med 2, D-89075 Ulm, Germany; Univ Ulm, Dept Radiol, D-89075 Ulm, Germany; Univ Ulm, Dept Gen Surg, D-89075 Ulm, Germany; Univ Ulm, Inst Clin Chem, D-89075 Ulm, Germany. CLINICA CHIMICA ACTA (DEC 2001) Vol. 314, No. 1-2, pp. 203-207. ISSN: 0009-8981. Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: For the **treatment** of aortic aneurysm, stent-graft implantation is an alternative method to open surgery. There is no study comparing both methods with regard to endotoxaemia, the acute phase cascade, and clinical outcome. Methods: In this prospective study, we enrolled 40 patients (34 males, 6 females; mean age 72.1 +/- 7.5 [58-92] years) with infrarenal abdominal aortic aneurysm who underwent aortic surgery. Comparable groups of patients were treated with open (n = 20) or endovascular (n = 20) stent-graft implantation. To characterize

the inflammatory response, plasma levels of **endotoxin**, **endotoxin**-neutralizing capacity (ENC), interleukin-6 (IL-6), C-reactive protein (CRP), and white blood cell count were determined. In all patients, measurements were performed on admission, skin suture, 4 h and from the first to fifth postoperative day. As parameters for the clinical outcome, we assessed daily temperature, lung function, pain, duration of postoperative hospital stay, and morbidity. Wilcoxon rank test was used for statistical analysis. Results: In both groups, a significant increase of **endotoxin** plasma levels and a decrease of ENC was found already after skin incision. IL-6 levels peaked 4 h postoperatively in both groups, whereas CRP rose at the first postoperative day, reaching a maximum at day 2. Conventionally operated patients had significantly higher plasma levels of **endotoxin**, IL-6, and CRP and lower ENC during and after surgery than patients with stent-graft implantation. Moreover, patients with endovascular stent grafting had significant less postoperative pain, less restriction of total vital capacity, a shorter hospital stay, and a lower morbidity. Conclusions: Endovascular stent grafting of infrarenal aortic aneurysm seems to be superior not only in terms of the inflammatory response but also in overall clinical outcome.

L4 ANSWER 13 OF 17 MEDLINE on STN DUPLICATE 5

2000486462. PubMed ID: 11036910. The **endotoxin**-lipoprotein hypothesis. Rauchhaus M; Coats A J; Anker S D. (Department of Clinical Cardiology, National Heart and Lung Institute, London, UK.. m.rauchhaus@ic.ac.uk) . Lancet, (2000 Sep 9) 356 (9233) 930-3. Ref: 31. Journal code: 2985213R. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The advent of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) has revolutionised the **treatment** of hypercholesterolaemia. Statin **treatment**, by lowering the atherogenic lipoprotein profile, reduces morbidity and mortality in patients with cardiovascular disease. **Treatment** with simvastatin causes a reduction of events of new-onset heart failure, but this may be attributable to properties other than its lipid-lowering effects. There is some evidence that lower serum cholesterol concentrations (as a surrogate for the totality of lipoproteins) relate to impaired survival in patients with **chronic heart failure** (CHF). Inflammation is a feature in patients with CHF and increased lipopolysaccharide may contribute substantially. We postulate that higher concentrations of total cholesterol are beneficial in these patients. This is potentially attributable to the property of lipoproteins to bind lipopolysaccharide, thereby preventing its detrimental effects. We hypothesise there is an optimum lipoprotein concentration below which lipid reduction would, on balance, be detrimental. We also propose that, in patients with CHF, a non-lipid-lowering statin (with ancillary properties such as immune modulatory and anti-inflammatory actions) could be as effective or even more beneficial than a lipid-lowering statin.

L4 ANSWER 14 OF 17 MEDLINE on STN DUPLICATE 6

1999285942. PubMed ID: 10359409. **Endotoxin** and immune activation in **chronic heart failure**: a prospective cohort study. Niebauer J; Volk H D; Kemp M; Dominguez M; Schumann R R; Rauchhaus M; Poole-Wilson P A; Coats A J; Anker S D. (Cardiac Medicine, National Heart and Lung Institute, Imperial College School of Medicine, London, UK.) Lancet, (1999 May 29) 353 (9167) 1838-42. Journal code: 2985213R. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: Immune activation in patients with **chronic heart failure** may be secondary to **endotoxin** (lipopolysaccharide) action. We investigated the hypothesis that altered gut permeability with bacterial translocation and endotoxaemia would be increased in patients with oedema secondary to congestive heart failure.

METHODS: We compared 20 patients who had **chronic heart failure** with recent-onset peripheral oedema (mean age 64 years [SD 10], New York Heart Association [NYHA] class 3.3 [0.7]), 20 stable non-oedematous patients with **chronic heart failure** (mean age 63 years [19], NYHA class 2.6 [0.7]), and 14 healthy volunteers (mean age 55 years [16]). Biochemical markers of endotoxaemia, inflammation, and immune activation were measured. Ten patients were studied within 1 week of complete resolution of oedema. Five patients survived longer than 6 months and were restudied again after remaining free of oedema for more than 3 months. FINDINGS: Mean **endotoxin** concentrations were higher in oedematous patients with **chronic heart failure** than in stable patients with **chronic heart failure** (0.74 [SD 0.45] vs 0.37 EU/mL [0.23], p=0.0009) and controls (0.46 EU/mL [0.21], p=0.02). Oedematous patients had the highest concentrations of several cytokines. After short-term diuretic **treatment**, **endotoxin** concentrations decreased from 0.84 EU/mL [0.49] to 0.45 EU/mL [0.21], p<0.05) but cytokines remained raised. After freedom of oedema for more than 3 months after oedema resolved, **endotoxin** concentrations remained unchanged from the previous visit (0.49 EU/mL [0.06], p=0.45). INTERPRETATION: Raised concentrations of **endotoxin** and cytokines are found in patients with **chronic heart failure** during acute oedematous exacerbation. Intensified diuretic **treatment** can normalise **endotoxin** concentrations. Our preliminary findings suggest that **endotoxin** may trigger immune activation in patients with **chronic heart failure** during oedematous episodes.

L4 ANSWER 15 OF 17 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1998:289861 The Genuine Article (R) Number: ZG811. Pathophysiologically relevant concentrations of tumor necrosis factor-alpha promote progressive left ventricular dysfunction and remodeling in rats. Bozkurt B; Kribbs S B; Clubb F J; Michael L H; Didenko V V; Hornsby P J; Seta Y; Oral H; Spinale F G; Mann D L (Reprint). VA Med Ctr, Cardiol Res 151C, 2002 Holcombe Blvd, Houston, TX 77030 USA (Reprint); Vet Adm Med Ctr, Dept Med, Cardiol Sect, Houston, TX 77211 USA; Baylor Coll Med, Huffington Ctr Aging, Dept Cell Biol, Houston, TX 77030 USA; Med Univ S Carolina, Dept Surg, Charleston, SC 29425 USA; Texas Heart Inst, Houston, TX 77025 USA. CIRCULATION (14 APR 1998) Vol. 97, No. 14, pp. 1382-1391. ISSN: 0009-7322. Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background-Although patients with heart failure express elevated circulating levels of tumor necrosis factor-alpha (TNF-alpha) in their peripheral circulation, the structural and functional effects of circulating levels of pathophysiologically relevant concentrations of TNF-alpha on the heart are not known.

Methods and Results-Osmotic infusion pumps containing either diluent or TNF-alpha were implanted into the peritoneal cavity of rats. The rate of TNF-alpha infusion was titrated to obtain systemic levels of biologically active TNF-alpha comparable to those reported in patients with heart failure (approximate to 80 to 100 U/mL), and the animals were examined serially for 15 days. Two-dimensional echocardiography was used to assess changes in left ventricular (LV) structure (remodeling) and LV function. Video edge detection was used to assess isolated cell mechanics, and standard histological techniques were used to assess changes in the volume composition of LV cardiac myocytes and the extracellular matrix, The reversibility of cytokine-induced effects was determined either by removal of the osmotic infusion pumps on day 15 or by **treatment** of the animals with a soluble TNF-alpha antagonist (TNFR:Fc). The results of this study show that a continuous infusion of TNF-alpha led to a time-dependent depression in LV function, cardiac myocyte shortening, and LV dilation that were at least partially reversible by removal of the osmotic infusion pumps or **treatment**

of the animals with TNFR:Fc.

Conclusions-These studies suggest that pathophysiologically relevant concentrations of TNF-alpha are sufficient to mimic certain aspects of the phenotype observed in experimental and clinical models of heart failure.

L4 ANSWER 16 OF 17 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1995:119368 The Genuine Article (R) Number: QF552. INCREASE OF MYOCARDIAL INHIBITORY G-PROTEINS IN CATECHOLAMINE-REFRACTORY SEPTIC SHOCK OR IN SEPTIC MULTIORGAN FAILURE. BOHM M (Reprint); KIRCHMAYR R; GIERSCHIK P; ERDMANN E. UNIV COLOGNE, MED UNIV & CLIN, DEPT INTERNAL MED 3, JOSEPH STELZMANN STR 9, D-50924 COLOGNE, GERMANY (Reprint). AMERICAN JOURNAL OF MEDICINE (FEB 1995) Vol. 98, No. 2, pp. 183-186. ISSN: 0002-9343. Publisher: CAHNERS PUBL CO, 249 WEST 17 STREET, NEW YORK, NY 10011. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB PURPOSE: The aim of the study was to investigate the mechanisms of myocardial catecholamine refractoriness in septic shock.

METHODS: The inhibitory guanine nucleotide-binding proteins (Gi alpha) were studied with pertussis toxin labeling and radioimmunologically in myocardium from patients who died while in catecholamine-refractory septic shock and from patients who died of noncardiac disease.

RESULTS: An increase by 62% (immunological Gi alpha) and 221% (pertussis toxin substrate) of myocardial Gi alpha was observed in patients with catecholamine-refractory shock compared with controls. The increases of Gi alpha were greater than those found in **chronic heart failure** reported earlier.

CONCLUSIONS: An increase in the expression of Gi alpha could also be important in conditions other than **chronic heart failure**, eg, septic shock. An increase of Gi alpha could play a pathophysiologically relevant role in catecholamine refractoriness in septic shock and could provide a target for pharmacologic **treatment** in this condition.

L4 ANSWER 17 OF 17 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1992:370486 The Genuine Article (R) Number: HY711. CLINICAL ASPECTS OF SEPTIC SHOCK AND COMPREHENSIVE APPROACHES TO **TREATMENT** IN DOGS AND CATS . WEEREN F R (Reprint); MUIR W W. OHIO STATE UNIV, SCH VET MED, DEPT VET CLIN SCI, COLUMBUS, OH 43210 (Reprint). JOURNAL OF THE AMERICAN VETERINARY MEDICAL ASSOCIATION (15 JUN 1992) Vol. 200, No. 12, pp. 1859-1870. ISSN: 0003-1488. Publisher: AMER VETERINARY MEDICAL ASSOC, 1931 N MEACHAM RD SUITE 100, SCHAUMBURG, IL 60173-4360. Language: English.

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=> s l2 and bile acid
L5            3 L2 AND BILE ACID

=> dup remove l5
PROCESSING COMPLETED FOR L5
L6            3 DUP REMOVE L5 (0 DUPLICATES REMOVED)

=> d l6 1-3 cbib abs

L6   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2005 ACS on STN
2005:1077916  Target solute binding compositions of core-shell polymer for
     therapeutic use and pharmaceutical compositions.  Charmot, Dominique;
     Fordtran, John; Chang, Han Ting; Connor, Eric; Liu, Mingjun; Klaerner,
     Gerrit (Symyx Therapeutics, Inc., USA).  U.S. Pat. Appl. Publ. US
     20050220889 A1 20051006, 26 pp.  (English).  CODEN: USXXCO.  APPLICATION:
     US 2004-813872 20040330.
AB   Use of the core-shell compns. for therapeutic and/or prophylactic benefits
     are discussed.  Examples of these include the treatment of
     phosphate imbalance disorders, hypertension, chronic
     heart failure, end stage renal disease, liver cirrhosis,
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chronic renal insufficiency, fluid overload, or Na overload.

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
2005:1075397 Methods and compositions for **treatment** of ion imbalances. Robert, Alpern; Buysse, Jerry; Chang, Han Ting; Charmot, Dominique; Cope, Michael James; Fordtran, John; Klaerner, Gerrit (Symyx Therapeutics, Inc., USA). U.S. Pat. Appl. Publ. US 20050220750 A1 20051006, 18 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-814527 20040330.
AB The present invention provides methods and compns. for the **treatment** of ion imbalances. In particular, the invention provides compns. comprising sodium-binding polymers and pharmaceutical compns. thereof. Methods of use of the polymeric and pharmaceutical compns. for therapeutic and/or prophylactic benefits are disclosed herein. Examples of these methods include the **treatment** of hypertension, **chronic heart failure**, end stage renal disease, liver cirrhosis, chronic renal insufficiency, fluid overload, or sodium overload.

L6 ANSWER 3 OF 3 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
2003:47605 The Genuine Article (R) Number: 630BL. Taurine modulates induction of cytochrome P450 3A4 mRNA by rifampicin in the HepG2 cell line. Matsuda H; Kinoshita K; Sumida A; Takahashi K; Fukuen S; Fukuda T; Takahashi K; Yamamoto I; Azuma J (Reprint). Osaka Univ, Grad Sch Pharmaceut Sci, 1-6 Yamadaoka, Suita, Osaka 5650871, Japan (Reprint); Osaka Univ, Grad Sch Pharmaceut Sci, Suita, Osaka 5650871, Japan; Mukogawa Womens Univ, Sch Pharmaceut Sci, Dept Pharmaceut, Nishinomiya, Hyogo, Japan. BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR CELL RESEARCH (16 DEC 2002) Vol. 1593, No. 1, pp. 93-98. ISSN: 0167-4889. Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Taurine is not only present in foods, tonics and nutrient drinks but is also used as a medicinal agent mainly for **treatment** of **chronic heart failure** and liver disease. However, little is known about its influence on drug-metabolizing enzymes, especially cytochrome P450 (CYP), in human. We examined whether. taurine could affect the expression of CYP3A4 mRNA in the presence or absence of rifampicin (RFP), which is a potent inducer of CYPs, with HepG2 cells. Taurine enhanced twice the induction of CYP3A4 mRNA by RFP, but did not affect the expression by itself. This effect was both concentration- and time-dependent. On the other hand, taurine did not affect the induction by phenobarbital. Taurine did not increase intracellular uptake of RFP. Therefore, we conclude that taurine is an enhancer for the induction of CYP3A4 by RFP. (C) 2002 Elsevier Science B.V. All rights reserved.

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=> s bile acid
L7       86596 BILE ACID

=> s l7 and chenodeoxycholic acid
L8        9861 L7 AND CHENODEOXYCHOLIC ACID

=> s l8 and ursodeoxycholic acid
L9        3193 L8 AND URSODEOXYCHOLIC ACID

=> s l9 and dehydrocholic acid
L10         63 L9 AND DEHYDROCHOLIC ACID

=> s l10 and cholic acid
L11         51 L10 AND CHOLIC ACID

=> s l11 and treatment
L12          4 L11 AND TREATMENT
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=> dup remove l12
PROCESSING COMPLETED FOR L12
L13 4 DUP REMOVE L12 (0 DUPLICATES REMOVED)

=> d l13 1-4 cbib abs

L13 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
2002:716924 Document No. 137:242183 Methods for modulating activity of the FXR nuclear receptor. Forman, Barry M.; Wang, Haibo (City of Hope, USA). U.S. Pat. Appl. Publ. US 2002132223 A1 20020919, 34 pp., Cont.-in-part of U.S. Ser. No. 533,862. (English). CODEN: USXXCO. APPLICATION: US 2001-971067 20011005. PRIORITY: US 1999-PV126334 19990326; US 2000-2000/533862 20000324.
AB The present invention relates to methods and compns. for modulating genes which are controlled by the FXR nuclear hormone receptor such as Cyp7a, Cyp8b, phospholipid transfer protein, ileal **bile acid** binding protein, sodium taurocholate cotransporter protein, liver fatty acid binding protein and bile salt export pump. In a preferred embodiment, the method involves modulation of the gene encoding Cyp7a, the enzyme responsible for a major pathway in the elimination of cholesterol. The invention also relates to methods for screening compds. which bind to and activate or inhibit the FXR nuclear hormone receptor and compds. which activate or inhibit the FXR nuclear hormone receptor.

L13 ANSWER 2 OF 4 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
97274150 EMBASE Document No.: 1997274150. Biotransformations on steroid nucleus of **bile acids.** Bortolini O.; Medici A.; Poli S.. Prof. O. Bortolini, Dipartimento di Chimica, Universita di Ferrara, Via Borsari 46, 44100 Ferrara, Italy. brl@dns.unife.it. Steroids Vol. 62, No. 8-9, pp. 564-577 1997.
Refs: 137.
ISSN: 0039-128X. CODEN: STEDAM
S 0039-128X(97)00043-3. Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 971002
AB The **bile acids** in mammals are all derivatives of 5β-cholan-26-oic acid. They represent the major quantitative pathway by which cholesterol is metabolized in the body. This article covers the microbial and enzymatic transformations of free, saturated **bile acids**, that kept unaltered the C-24 cyclopentane-perhydrophenantrene nucleus. The **bile acids** that have been considered include the primary cholic and **chenodeoxycholic acids**, the secondary deoxycholic and lithocholic acids as well as the relevant dehydrocholic, ursocholic and **ursodeoxycholic acids.** Among the **bile acid** biotransformations, attention is paid to reactions that lead to pharmaceutically significant compounds. This is the case of 7α-hydroxy epimerization of **chenodeoxycholic acid** to **ursodeoxycholic acid**, currently used for cholesterol gallstone dissolution therapy and in the **treatment** of cholestatic liver diseases. Emphasis has placed on reporting reactions that may be of general interest and on the practical aspects of work in the field of biotransformations.

L13 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
1987:131524 Document No. 106:131524 Cholagogous effect of **ursodeoxycholic acid** in cholestatic factor-induced intrahepatic cholestasis. Miyajima, Keiji; Mizoguchi, Yasuhiro; Sakagami, Yoshihide; Kobayashi, Kenzo; Yamamoto, Sukeo; Morisawa, Seiji (Med. Sch., Osaka City Univ., Osaka, Japan). Kanzo, 27(11), 1578-83 (Japanese) 1986. CODEN: KNZOAU. ISSN: 0451-4203.
AB Intrahepatic cholestasis induced by injection of cholestatic factor into the mesenteric vein of rats was improved by simultaneous administration of **ursodeoxycholic acid** [128-13-2] and the cholestatic

factor. Various **bile acids** such as **chenodeoxycholic acid** [474-25-9], **cholic acid** [81-25-4], deoxycholic acid [83-44-3] or **dehydrocholic acid** [81-23-2] exerted a similar but less pronounced cholagogous effect. These effects were recognized in both normal rats and those with cholestatic factor-induced intrahepatic cholestasis. **Ursodeoxycholic acid** had the strongest cholagogic activity, indicating that it may be applicable for the **treatment** of intrahepatic cholestasis.

L13 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN
1966:54030 Document No. 64:54030 Original Reference No. 64:10141e-g Effect of various dietary **bile acids** on nutrient absorption and on liver size in chicks. Eyssen, H.; Vandeputte, M.; Evrard, E. (Univ. Louvain, Belg.). Archives Internationales de Pharmacodynamie et de Therapie, 158(2), 292-306 (English) 1965. CODEN: AIPTAK. ISSN: 0003-9780.
AB Lithocholic acid (I) depressed the growth, caused malabsorption of fats, impaired efficiency of feed utilization, and increased in liver weight after 2 weeks of **treatment** in 3-week-old cockerels. I reduced body-weight gain by 20% to 40% and increased the serum cholesterol and total concns. of liver cholesterol 3-fold. 3-Oxocholanic acid caused an identical syndrome. I caused necrosis of hepatocytes, followed by proliferation of cholangiocytes and cholangiofibrosis in liver. Ascites and fibrinous exudation were present in the peritoneal cavity after 1-month feeding of I. **Cholic acid**, **chenodeoxycholic acid**, **dehydrocholic acid**, hyodeoxycholic acid, and **ursodeoxycholic acid** were devoid of liver toxicity, improved the intestinal absorption of fat, and did not significantly affect concns. of serum cholesterol or liver cholesterol.

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=> s l8 and treatment
L14        1940 L8 AND TREATMENT

=> s l14 and human
L15        1174 L14 AND HUMAN

=> s l15 and heart
L16          12 L15 AND HEART

=> dup remove l16
PROCESSING COMPLETED FOR L16
L17           8 DUP REMOVE L16 (4 DUPLICATES REMOVED)

=> d l17 1-8 cbib abs

L17 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
2004:251565 Document No. 140:354367 Expression and activation of the farnesoid X receptor in the vasculature. Bishop-Bailey, David; Walsh, Desmond T.; Warner, Timothy D. (Cardiac, Vascular, Research, William Harvey Research Institute, Barts and the London, Queen Mary University of London, London, EC1M 6BQ, UK). Proceedings of the National Academy of Sciences of the United States of America, 101(10), 3668-3673 (English) 2004. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.
AB The farnesoid X receptor/**bile acid** receptor (FXR) is a recently discovered member of the nuclear hormone superfamily. FXR ligands have been proposed as targets in cardiovascular disease, regulating cholesterol metabolism and **bile acid** transport and metabolism in the liver and gastrointestinal tract. When the authors used a **human** cardiovascular tissue array, the authors found that FXR is expressed in a variety of normal and pathol. **human** tissue. Particularly high levels of FXR were found in the vasculature and in a number
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of different metastatic cancers, as well as the previously identified target tissues of the liver, small intestine, and kidney. In vitro, FXR is present in rat and **human** vascular smooth muscle cells. When treated with a range of FXR ligands, vascular smooth muscle cells undergo apoptosis in a manner that correlates with the ligands' ability to activate FXR. Furthermore, FXR activators induce mRNA for the FXR target genes, phospholipid transfer protein, and the small heterodimer partner. FXR therefore is a functional protein in the vasculature that may provide a direct target for the **treatment** of proliferative and dyslipidemic diseases.

L17 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2005 ACS on STN
2004:294110 Document No. 141:70828 Cholic acid supplementation enhances cholesterol absorption in **humans**. Woollett, Laura A.; Buckley, Donna D.; Yao, Lihang; Jones, Peter J. H.; Granholm, Norman A.; Tolley, Elizabeth A.; Tso, Patrick; Heubi, James E. (Department of Pathology and Laboratory Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, USA). Gastroenterology, 126(3), 724-731 (English) 2004. CODEN: GASTAB. ISSN: 0016-5085. Publisher: W. B. Saunders Co..
AB Background & Aims: Qual. and quant. changes in intralumenal **bile acid** composition may alter cholesterol absorption and synthesis and low-d. lipoprotein (LDL) receptor expression. The role of cholic acid (CA) in cholesterol absorption in **humans** remains unclear and, thus, was examined in the current study. Methods: In a crossover design outpatient study, 12 adults aged 24-36 yr took 15 mg/kg/day (CA) or no **bile acid** supplement (control) while being fed a controlled diet (AHA **heart**-healthy diet). A liquid meal of defined composition was given on day 14 of the diet, and lumenal samples were collected. Thereafter, cholesterol absorption and cholesterol fractional synthetic rate (FSR) were assessed by stable isotopic methods from days 16 to 20. Results: With CA **treatment**, bile was enriched significantly with CA ($P < 0.0004$) to 60.2% ± 2.4% (mean ± SEM) compared with 43.3% ± 2.4% for controls. CA plus diet **treatment** significantly increased ($P = 0.013$) cholesterol absorption (72.6% ± 2.9%) compared with diet **treatment** alone (60.4% ± 2.9%). Percentage micellar cholesterol was increased by CA plus diet **treatment** vs. diet alone after meal ingestion ($P = 0.004$). Plasma total and high-d. lipoprotein (HDL) and LDL cholesterol was unchanged with CA **treatment**. Conclusions: Thus, enrichment in lumenal bile with CA results in an increase in cholesterol absorption, an effect potentially mediated by enhanced cholesterol solubilization in micelles.

L17 ANSWER 3 OF 8 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
2003314727 EMBASE Activation of muscarinic receptor signaling by **bile acids**: Physiological and medical implications. Raufman J.-P.; Cheng K.; Zimniak P.. Dr. J.-P. Raufman, Div. of Gastroenterol./Hepatology, Univ. of Maryland School of Medicine, 22 South Greene Street, Baltimore, MD 21201-1595, United States. Digestive Diseases and Sciences Vol. 48, No. 8, pp. 1431-1444 1 Aug 2003.
Refs: 118.
ISSN: 0163-2116. CODEN: DDSCDJ
Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 20030821
AB Besides their known physiological actions, **bile acids** are signaling molecules that alter cell function by interacting with muscarinic and nuclear receptors. **Bile acid** interaction with nuclear receptors modulates **bile acid** and cholesterol metabolism, whereas the potential consequences of muscarinic receptor activation are much broader. This review examines recent discoveries regarding **bile acid** interaction with muscarinic receptors. Selective and functional **bile acid** interaction has been reported with M3 receptors expressed in guinea pig gastric chief cells, **human** colon cancer cells, and

transfected Chinese hamster ovary cells. Interaction of **bile acids** with chief cells may contribute to mucosal damage and other pathophysiological consequences of bile reflux. **Bile acid**-induced stimulation of muscarinic receptors on colon cancer cells may contribute to cellular proliferation and neoplasia. Potential consequences of **bile acid** interaction with muscarinic receptors on gastrointestinal myocytes, biliary epithelium, vascular endothelium and dermal neurons are discussed. Elucidation of molecular mechanisms underlying interaction of **bile acids** with muscarinic receptors may suggest new **treatments** for conditions that result from such interactions.

L17 ANSWER 4 OF 8 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

97270503 EMBASE Document No.: 1997270503. Effect of dobutamine on serum **bile acid** levels in patients with cirrhosis. Konno T.; Tada K.; Akamatsu K.. Dr. K. Tada, Third Department Internal Medicine, Ehime University School of Medicine, Shitsukawa, Shigenobu, Onsen-gun, Ehime 791-02, Japan. Current Therapeutic Research - Clinical and Experimental Vol. 58, No. 8, pp. 515-524 1997.

Refs: 31.

ISSN: 0011-393X. CODEN: CTCEA

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 970925

AB To investigate whether improving hepatic blood flow is effective as a **treatment** for cirrhosis we measured cardiac output and hepatic blood flow in eight patients with cirrhosis and hepatocellular carcinoma (5 women and 3 men, aged 51 to 64 years) who were given dobutamine intravenously through a peripheral vein. The relationship between changes in hepatic blood flow and changes in total **bile acid** concentration in the peripheral blood were assessed. Hepatic blood now was measured by using the xenon 133 gas clearance method with a catheter positioned in the portal vein. Dobutamine infusion increased cardiac output and hepatic blood flow to 133.9% and 111.4% of preinfusion values, respectively, and decreased total serum **bile acid** concentration 120 minutes after the start of infusion to 59.0% of the pretreatment value. The **bile acids**, in descending order of the highest percent decrease, were ursodeoxycholic, cholic, deoxycholic, chenodeoxycholic, and lithocholic; however, there were no significant differences between the free, glycine-conjugated, and taurine-conjugated forms. The percent decrease in total serum **bile acids** was significantly correlated with the percent increase in hepatic blood flow. These findings suggest that increasing blood flow could be an effective way to decrease total serum **bile acid** levels and thus possibly promote liver function in patients with cirrhosis.

L17 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 1

96314245. PubMed ID: 8724029. Cyclosporin A-mediated cholestasis in patients with chronic hepatitis after **heart** transplantation. Myara A; Cadranel J F; Dorent R; Lunel F; Bouvier E; Gerhardt M; Bernard B; Ghoussoub J J; Cabrol A; Gandjbakhch I; Opolon P; Trivin F. (Department of Biochimie, Hopital Saint-Joseph, Paris, France.) European journal of gastroenterology & hepatology, (1996 Mar) 8 (3) 267-71. Journal code: 9000874. ISSN: 0954-691X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Viral chronic hepatitis often occurs in **heart** transplant recipients receiving cyclosporin. . This essential immunosuppressive drug may induce cholestasis. We investigated the effect of **treatment** with cyclosporin on serum conjugated **bile acids** in patients with chronic hepatitis developing after **heart** transplantation. Fifty-nine patients were studied: 17 with chronic hepatitis, 15 **heart** transplant patients with normal alanine aminotransferase activity, and 27 **heart** transplant patients with chronic hepatitis, the last two groups receiving cyclosporin. Hepatic

biochemical tests and total **bile acid** concentration were determined on fasting blood samples. The individual glyco- and tauroconjugated **bile acids** were quantified by high-performance liquid chromatography and direct spectrometry. In patients taking cyclosporin the bilirubin concentration and the alkaline phosphatase activity were increased only when hepatitis was present, in association with a slight increase in cholic acid level (5.13 microM vs. 0.68 microM; P < 0.01). Conjugated lithocholate concentration was dramatically higher when hepatitis and immunosuppression with cyclosporin were associated (1.17 microM vs. 0.03 and 0.04 microM; P < 0.01). Chenodeoxycholate was the main circulating **bile acid** only in the **heart** transplant patients treated with cyclosporin but without hepatitis. These results suggest that the mechanisms which explain the cyclosporin-associated modifications of the **bile acid** pool are different according to the presence or absence of hepatitis. The occurrence of hepatitis in patients on cyclosporin led to an increase in serum lithocholate and primary **bile acid** concentrations. Further studies are required to assess the effect of ursodeoxycholic acid for this cholestasis.

L17 ANSWER 6 OF 8 MEDLINE on STN DUPLICATE 2

96033638. PubMed ID: 7482380. [**Bile acids** in liver diseases--current indications]. Gallensauren bei Lebererkrankungen--neue Indikationen. Stiehl A. (Medizinische Universitatsklinik, Heidelberg.) Therapeutische Umschau. Revue therapeutique, (1995 Oct) 52 (10) 682-6. Ref: 29. Journal code: 0407224. ISSN: 0040-5930. Pub. country: Switzerland. Language: German.

AB Ursodeoxycholic acid (UDCA) has beneficial effects in cholestatic diseases such as primary biliary cirrhosis, primary sclerosing cholangitis and cholestasis of pregnancy. In chronic hepatitis and alcoholic hepatitis, an effect of UDCA is uncertain. After organ transplantation (liver, bone, **heart**), favorable effects of UDCA which await confirmation were observed. UDCA very likely has a beneficial effect in children with Byler's and Alagille's syndrome, extrahepatic biliary atresia after the Kasai procedure and in cholestasis of cystic fibrosis. Unclear is the effect of UDCA in benign intermittent cholestasis (Summerskill-Tygstrup syndrome). Children with cholestasis and inborn errors of **bile acid** synthesis need additional administration of a primary **bile acid** (cholic acid, **chenodeoxycholic acid**). UDCA **treatment** in general does not lead to definitive cure of the disease but to improvement of laboratory parameters and possibly of symptoms and liver histology, and liver transplantation may be postponed to a later time point.

L17 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 3

88117193. PubMed ID: 2828498. Modulation of low density lipoprotein receptor activity by **bile acids**: differential effects of chenodeoxycholic and ursodeoxycholic acids in the hamster. Malavolti M; Fromm H; Ceryak S; Roberts I M. (Department of Medicine, George Washington University Medical Center, Washington, DC 20037.) Journal of lipid research, (1987 Nov) 28 (11) 1281-95. Journal code: 0376606. ISSN: 0022-2275. Pub. country: United States. Language: English.

AB Hamsters were fed **chenodeoxycholic acid** (CDC), ursodeoxycholic acid, (UDC), or no **bile acid.** [14C]Sucrose-labeled hamster low density lipoprotein (LDL) and methylated **human** LDL were infused intravenously to study LDL receptor-dependent and LDL receptor-independent organ uptake, respectively, of LDL. Biliary CDC increased during both CDC and UDC **treatment.** The UDC enrichment of bile after UDC feeding was relatively small. **Bile acid** synthesis was suppressed after both **bile acid treatments.** Under the condition of an acute bile fistula, the hamster LDL uptake increased in the liver, **heart**, and adrenals in the CDC-treated animals. During an intact enterohepatic circulation, the hepatic uptake of hamster LDL, which accounted for a major portion of the total uptake, was

increased after UDC **treatment**. The hamster LDL uptake in the colon, which represented only a small fraction of the total uptake, increased after CDC **treatment**. When hamster LDL was infused at increasing concentrations, its uptake was significantly higher in the UDC-treated than in the control and CDC-treated animals. The methylated **human** LDL uptake showed no significant changes in the different **treatment** groups under either experimental condition. The study shows significantly different effects of CDC and UDC on LDL receptor activity. Since these differences are expressed in spite of a similar suppression of **bile acid** synthesis, UDC may directly influence LDL receptor activity.

L17 ANSWER 8 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
1981:158109 Document No.: PREV198171028101; BA71:28101. COMPARISON OF THE EFFECTS BETWEEN URSO DEOXY CHOLIC-ACID AND CHENO DEOXY CHOLIC-ACID ON LIVER FUNCTION AND STRUCTURE AND **BILE ACID** COMPOSITION IN THE RHESUS MONKEY MACACA-MULATTA. SARVA R P [Reprint author]; FROMM H; FARIVAR S; SEMBRAT R F; MENDELOW H; SHINOZUKA H; WOLFSON S K. MONTEFIORE HOSP, 3459 FIFTH AVE, PITTSBURGH, PA 15213, USA. Gastroenterology, (1980) Vol. 79, No. 4, pp. 629-636.
CODEN: GASTAB. ISSN: 0016-5085. Language: ENGLISH.

AB The hepatotoxic potential of the cholelitholytic **bile acids**, chenodeoxycholic (chenic) and ursodeoxycholic acids, was compared in the rhesus monkey [M. mulatta.] A placebo-controlled **treatment** trial with 40 and 120 mg/kg per day doses of chenic acid and ursodeoxycholic acid, respectively, was conducted in 20 animals. Chenic and ursodeoxycholic acids induced comparable abnormalities of liver function and structure. Liver biopsies, performed before and after 6 mo. of **treatment**, showed the development of distinct light microscopic changes, including inflammation, fibrosis and ductular proliferation in the portal fields as well as lobular rearrangement with formation of septa and regenerative nodules. EM confirmed light microscopy, but showed no specific changes of cell organelles. Light microscopic examination of the kidneys, lungs, **heart**, intestine and brain in 10 monkeys, which were sacrificed after 6 mo. of controlled **bile acid treatment**, showed no abnormalities. Biliary lithocholic acid, all of which was unsulfated, increased several-fold to comparable levels in the **bile acid** -treated groups. Follow-up studies 6 mo. after termination of **bile acid treatment** showed normalization of liver function tests and of **bile acid** composition as well as a considerable improvement of the histologic abnormalities. The restitution of normal liver structure was incomplete, with fibrosis and mild inflammation persisting in the portal fields. In this primate species, chenic and ursodeoxycholic acids apparently have comparable hepatotoxic effects, which are associated with similar increases of unsulfated lithocholic acid in bile. [Chenodeoxycholic (chenic) acid and its 7β-epimer, ursodeoxycholic acid, are presently being studied for their efficacy and safety in the dissolution of cholesterol gallstones in **humans**.].

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=> s l7 and urodeoxycholic acid
L18          11 L7 AND URODEOXYCHOLIC ACID

=> dup remove l18
PROCESSING COMPLETED FOR L18
L19          11 DUP REMOVE L18 (0 DUPLICATES REMOVED)

=> d l19 1-11 cbib abs

L19  ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2005 ACS on STN
2002:757207   Document No. 138:13726  Changes in bile acid
     composition and effect on cytolytic activity of fecal water by
     ursodeoxycholic acid administration: a placebo-controlled cross-over
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intervention trial in healthy volunteers. van Gorkom, B. A. P.; van der Meer, R.; Boersma-van Ek, W.; Termont, D. S. M. L.; de Vries, E. G. E.; Kleibeuker, J. H. (Depts. of Gastroenterology and Medical Oncology, University Hospital, Groningen, Neth.). Scandinavian Journal of Gastroenterology, 37(8), 965-971 (English) 2002. CODEN: SJGRA4. ISSN: 0036-5521. Publisher: Taylor & Francis.

AB Background: Ursodeoxycholic acid (UDCA) has been shown to affect membrane-damaging effects of **bile acids** in vitro and fecal **bile acid** composition in rats. This study evaluates the effect of UDCA on fecal **bile acid** composition and on cytolytic activity of fecal water in man to clarify the potential chemopreventive role of UDCA for colorectal cancer. Methods: In this placebo-controlled crossover intervention trial, the effect of 900 mg/day UDCA orally in 15 healthy volunteers was studied. At the end of each 4-wk period, 72 h feces were collected. Total and individual **bile acids** in feces were determined by gas chromatog. and soluble **bile acids** were analyzed by high-performance liquid chromatog. Cytolytic activity of fecal water was measured using an erythrocyte lysis assay. Results: In feces, the percentages of primary **bile acids** --cholic acid (CA) and chenodeoxycholic acid (CDCA)-and of secondary **bile acid**-deoxycholic acid (DCA)-decreased after supplementation with UDCA, whereas those of UDCA and LCA increased from 2.7 ± 0.4% to 23.7 ± 2.6%, P < 0.0001 and from 26.2 ± 1.2% to 49.4 ± 1.8%, P < 0.0001 resp. The concns. of these two **bile acids** in fecal water also increased after UDCA administration from 7.8 ± 1.9 μmol/l to 47.0 ± 6.7 μmol/l (UDCA), P < 0.0001 and from 2.5 ± 0.6 μmol/l to 18.3 ± 4.1 μmol/l (LCA), P < 0.002, resp. Cytolytic activity of fecal water was not affected by UDCA. Conclusion: These results do not support a protective effect of UDCA supplementation against colorectal cancer in man.

L19 ANSWER 2 OF 11 MEDLINE on STN

92009472. PubMed ID: 1916489. Effect of ursodeoxycholic acid treatment on ileal absorption of **bile acids** in man as determined by the SeHCAT test. Eusufzai S; Ericsson S; Cederlund T; Einarsson K; Angelin B. (Metabolism Unit, Karolinska Institutet, Huddinge University Hospital, Huddinge, Sweden.) Gut, (1991 Sep) 32 (9) 1044-8. Journal code: 2985108R. ISSN: 0017-5749. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The effects of **urodeoxycholic acid** on ileal absorption of **bile acids** and on serum **bile acid** and lipoprotein concentrations were studied. Eight healthy subjects were investigated. The gamma emitting **bile acid** analogue, SeHCAT, was given orally and its fractional catabolic rate and seven day retention were assessed by repeated external counting over the upper abdomen during the next seven days. Ursodeoxycholic acid was then given orally at a dose of 15 mg/kg/day for three weeks and the study was repeated during treatment. The fractional catabolic rate increased by 64% (mean (SD), 0.333 (0.159) v 0.203 (0.061)/day; p less than 0.05) and seven day retention decreased by 44% (15(10) v 27(10)%, p less than 0.001), indicating **bile acid** malabsorption. Total serum cholesterol fell from 5.79 (1.22) to 5.50 (1.18) mmol/l (p = 0.05), while serum ursodeoxycholic acid increased 22 fold (7.87 (2.67) v 0.34 (0.24) mumol/l, p less than 0.001). Five of the subjects continued taking 30 mg/kg/day of ursodeoxycholic acid for one week and showed an increase in fractional catabolic rate of 81% (0.300 (0.091) v 0.166 (0.037)/day; p less than 0.05) and a fall in seven day retention of 50% (16 (12) v 32 (8)%, p less than 0.01). There were significant reductions in total cholesterol (5.36 (1.71) v 6.08 (1.47) mmol/l; p less than 0.05) and low density lipoprotein cholesterol (3.70 (1.33) v 4.58 (1.16) mmol/l; p less than 0.05). The results support the concept tht ursodeoxycholic acid treatment interferes with the absorption of endogenous **bile acids**, and emphasise the beneficial effects of this treatment of lipoprotein concentrations in man.

L19 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
1991:114550 Document No. 114:114550 Metabolism of 3,7-dioxo-5β-cholanoic acid in the biliary fistula rodents and rabbits. Miki, Shigeo; Asanuma, Yusuke; Une, Mizuho; Hoshita, Takahiko (Sch. Med., Kyushu Univ., Fukuoka, 812, Japan). Journal of Pharmacobio-Dynamics, 13(10), 637-46 (English) 1990. CODEN: JOPHDQ. ISSN: 0386-846X.

AB Intestinal absorption and metabolism of 3,7-dioxo-5β-cholanoic acid, were studied in the bile fistula rats, hamsters, guinea pigs and rabbits. The influence of dose (1 and 100 mg/kg) on the absorption and the metabolism was also estimated The dioxo **bile acid** was absorbed efficiently from the intestine and quickly excreted into bile in these animals. Large dose did not retard the absorption rate and showed a significant choleretic effect for a few hours. Species differences were observed in the metabolism of this compound In hamsters and guinea pigs, most of the metabolites in the bile were conjugated with either taurine or glycine. The proportion of **bile acids** amidated with glycine, whereas in rabbits, glycine conjugates were the only recovered metabolites; unconjugated metabolites were also detected in the bile of the rodents, and the proportion of them rose to 17-29% after the administration of 100 mg/kg quantities. A small part of unchanged 3,7-dioxo-5β-cholanoic acid was excreted into the bile as both the conjugated and unconjugated forms in these animals. The greater part of this compound administered was metabolized to 7-ketolithocholic acid, chenodeoxycholic acid and **urodeoxycholic acid.** In hamsters and guinea pigs, chenodeoxycholic acid was a greater metabolite of this compound than ursodeoxycholic acid, while in rats and rabbits, the amount of ursodeoxycholic acid exceeded that of chenodeoxycholic acid. In rats, the resulting dihydroxy **bile acids** were further metabolized to α- and β-muricholic acids.

L19 ANSWER 4 OF 11 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
84077482 EMBASE Document No.: 1984077482. Effect of ursodeoxycholic acid treatment on intestinal absorption of triglycerides in man. Einarsson K.; Bjorkhem I.; Eklof R.; et al.. Department of Medicine, Karolinska Institute at Huddinge University Hospital, S-14186 Huddinge, Sweden. Scandinavian Journal of Gastroenterology Vol. 19, No. 2, pp. 283-288 1984.
CODEN: SJGRA4
Pub. Country: Norway. Language: English.

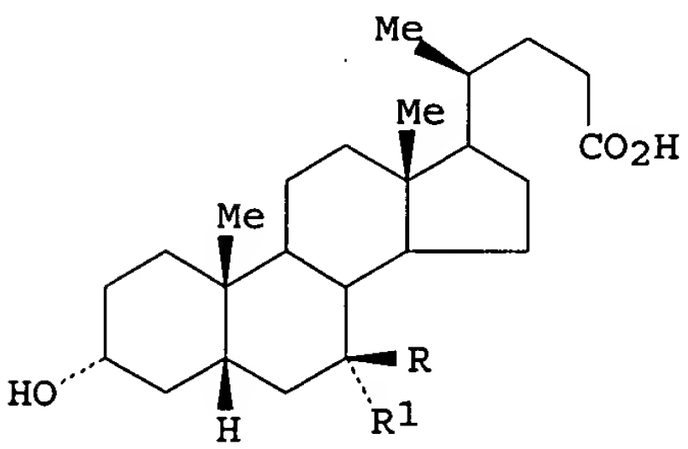
ED Entered STN: 911210

AB The aim of the present study was to evaluate whether treatment with **urodeoxycholic acid** (UDCA) may affect the absorption of dietary fat in man. Fifteen healthy subjects volunteered for the study. They were treated with UDCA in a daily dose of 15 mg/kg body weight for 4 weeks. Before and during treatment fat absorption was measured with a 14C-triolein breath test. In addition, fasting serum **bile acids** were measured in 11 of the subjects. The maximum specific activity of 14CO2 was not significantly changed during the treatment period. However, the cumulative output of 14CO2 during a 6-h period was decreased by about 25% ($p < 0.03$). Several subjects with decreased outputs also lost 1-2 kg of body weight during the study period. UDCA treatment raised the serum level of **bile acid** from 0.18 ± 0.11 μmol/l to 5.98 ± 1.08 μmol/l. The concentrations of the other **bile acids** were not significantly changed. It is suggested that UDCA treatment may in some patients be associated with an impaired fat absorption. Whether this effect is of any clinical importance remains to be elucidated.

L19 ANSWER 5 OF 11 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
83058114 EMBASE Document No.: 1983058114. Effect of litholytic **bile acids** on cholesterol absorption in gallstone patients. LaRusso N.F.; Thistle J.L.. Gastroenterol. Unit, Div. Gastroenterol., Mayo Clin.,

Rochester, MN 55905, United States. Gastroenterology Vol. 84, No. 2, pp. 265-271 1983.
CODEN: GASTAB
Pub. Country: United States. Language: English.
ED Entered STN: 911209
AB We measured intestinal absorption of cholesterol by a plasma isotope ratio method and determined biliary **bile acid** and lipid composition of fasting gallbladder bile in 5 gallstone patients before therapy and during two randomized treatment periods with chenodeoxycholic or ursodeoxycholic acid (13 mg/kg·day). During chenodeoxycholic acid ingestion, biliary **bile acids** were composed predominantly (84%) of conjugates of chenodeoxycholic acid. During ursodeoxycholic acid administration, conjugates of ursodeoxycholic acid constituted half the **bile acid** pool (49%). Fasting gallbladder bile was supersaturated in cholesterol before treatment, but became unsaturated during administration of both chenodeoxycholic and ursodeoxycholic acids. In spite of these marked changes in biliary **bile acid** and lipid composition, cholesterol absorption was not significantly different before (45.4 ± 4.3%, mean ± SEM) or after chenodeoxycholic (42.7 ± 5.1%) or ursodeoxycholic (46.8 ± 3.7%) acid ingestion. We conclude that chenodeoxycholic and **urodeoxycholic acids** unsaturate bile in cholesterol and dissolve gallstones by a mechanism other than the suppression of intestinal absorption of cholesterol.

L19 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
1982:193413 Document No. 96:193413 Hepatotoxicity of **bile acids** in rabbits. Ursodeoxycholic acid is less toxic than chenodeoxycholic acid. Miyai, Katsumi; Javitt, Norman B.; Gochman, Nathan; Jones, H. Martin; Baker, David (Sch. Med., Univ. California, La Jolla, CA, USA). Laboratory Investigation, 46(4), 428-37 (English) 1982.
CODEN: LAINAW. ISSN: 0023-6837.
GI



I, R=OH, R^1=H
II, R=H, R^1=OH

AB Male rabbits were fed regular laboratory chow containing ursodeoxycholic acid (I)
[128-13-2] chenodeoxycholic acid (II) [474-25-9], or lithocholic acid [434-13-9] at a concentration of 0.5% (weight weight) for 14 days. The mortality rate
was highest (6 of 12) in the lithocholate group, intermediate (2 or 8) in the II group, and lowest (0 of 6) in the I group. Light microscopy of the liver revealed fibrosis, inflammation, and bile duct proliferation in the portal regions in the 3 exptl. groups; however, the lesions in the lithocholate and II groups were more severe and often associated with periportal extension of fibrosis and focal necrosis of the parenchyma. In addition, electron microscopy revealed distortion of bile canaliculi, conspicuous bundles of intermediate-sized filaments, expansion of pericanalicular cytoplasmic matrix due to apparent accumulation of microfilaments, prominence of lysosomes, and fragmentation of cisternae of the rough endoplasmic reticulum. These ultrastructural changes were less marked and often absent in the I group. The serum L-alanine

aminotransferase activity increased 5-6-fold in the lithocholate and II groups, whereas it remained <2-fold of the control level in the I group on day 14. The serum lithocholate concentration was markedly elevated to comparable
levels in all 3 groups, whereas I was highly increased in the I group but undetectable in the other groups at the time of sacrifice. Thus (1) although the oral administration of 3 **bile acids**
induces hepatic injuries in the rabbit, I causes less severe injury than do the other 2, (2) the advantage of I vs. II is probably relative rather than absolute, (3) lithocholate formed through metabolic conversion from I may be responsible for the most part for hepatotoxicity, and (4) it is possible that the concurrent presence of I may mitigate lithocholate's hepatotoxicity.

L19 ANSWER 7 OF 11 EMBASE
81008049 EMBASE Document No.: 1981008049. Plasma disappearance of serum **bile acids** in patients with constitutional
hyperbilirubinemias and constitutional ICG excretory defect. Nambu M.; Namihisa T.; Yamashiro Y.; et al.. Dept. Gastroenterol., Int. Med., Cent. Hosp. Japanese Nat. Railway, Tokyo, Japan. Japanese Journal of Gastroenterology Vol. 77, No. 9, pp. 1369-1377 1980.
CODEN: NIPAA4
Pub. Country: Japan. Language: Japanese. Summary Language: English.
ED Entered STN: 911209
AB We observed the disappearance of **bile acids** in serum
following an oral administration of 300 mg ursodeoxycholic acid (UDCA) in 7 patients with constitutional hyperbilirubinemias, in one patient with a constitutional ICG excretory defect and in 5 healthy subjects. Serum **bile acids** were determined using gas liquid
chromatography. A secondary rise of UDCA during plasma disappearance was revealed in patients with Dubin-Johnson syndrome and in a patient with unconjugated hyperbilirubinemia associated with delayed plasma BSP clearance. In 4 patients with Rotor's syndrome the plasma disappearance of UDCA was divided into two types, two patients showed parabolic disappearance curve and two other patients showed an almost normal disappearance curve. In the patient with a constitutional ICG excretory defect the disappearance of UDCA was delayed after reaching a maximal level at 60 minutes after administration. There was no similar disappearance of other **bile acids** after an
administration of UDCA in these disorders. There was no correlation between fasting serum **bile acids** concentrations and
patterns of the UDCA plasma disappearance. We report a new **bile acid**, 3β, 7β-dihydroxy-5β-cholan-24-oic acid(3,
7β-cholanoic acid), and this **bile acid** in serum
was determined before and after an administration of UDCA. The fasting level of this **bile acid** was 0.08+-0.07 (mean+-SD)
μg/ml in 5 healthy subjects. In patients with constitutional hyperbilirubinemias serum concentrations of this **bile**
acid were distributed in normal range. The highest level (0.24 μg/ml) was found in the patient with a constitutional ICG excretory defect. There was no definite change of serum 3β, 7β-cholanoic acid concentrations following oral administration of UDCA.

L19 ANSWER 8 OF 11 EMBASE
79210599 EMBASE Document No.: 1979210599. Transformation of **bile**
acids by members of the Enterobacteriaceae. Imamura T.; Sakamoto N.; Tamaki M.; Hirano S.. Dept. Microbiol., Coll. Hlth. Sci., Ryukyus Univ., 585 Yogi, Naha, Japan. Japanese Journal of Bacteriology Vol. 34, No. 3, pp. 513-520 1979.
CODEN: NSKZAM
Pub. Country: Japan. Language: Japanese. Summary Language: English.
AB 89 Strains of microorganisms belonging to the family Enterobacteriaceae were examined for ability to deconjugate taurocholic acid (TCA) and to

metabolize cholic acid (CA) and chenodeoxycholic acid (CDCA). They were grown in the presence of each **bile acid** in several kinds of modified peptone-yeast extract broth. After aerobic or anaerobic incubation for a definite period of time, the culture fluids were collected and analyzed quantitatively for **bile acid** composition by gas-liquid chromatography. The 89 strains consisted of 15 strains of Escherichia coli, 12 of Shigella, 56 of Salmonella, and 6 of miscellaneous species. None of them were able to split TCA. Fourteen E. coli strains and two Shigella strains were active in causing 7α-dehydrogenation of CA and CDCA as the sole reaction involved. Both acids were metabolized at a more or less similar rate. A variety in the composition of basal medium caused little change in the rate and extent of transformation. The reaction occurred to a considerable degree in anaerobic cultures, though enhanced in aerobic cultures. A reversible conversion was evidenced between CDCA and its oxidation product, 7-ketolithocholic acid (7KL). The reductive conversion of 7KL into CDCA proceeded to a far less extent than the oxidative process of CDCA into 7KL. No epimerizing reduction of 7 KL to **urodeoxycholic acid** (UDCA) was observed. No strains were capable of decomposing UDCA. The 7α-dehydrogenation took place in the CDCA moiety in its conjugates without deconjugation.

L19 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
1980:37467 Document No. 92:37467 Transformation of **bile acids** by isolates from rabbit intestine. Mukai, Hiroshi (Fac. Med., Kagoshima Univ., Kagoshima, Japan). Kagoshima Daigaku Igaku Zasshi, 31(1), 115-25 (Japanese) 1979. CODEN: KDIZAA. ISSN: 0368-5063.

AB The metabolism of **bile acids** was examined with 52 bacterial strains, 27 gram-neg. anaerobic bacilli, 9 gram-pos. anaerobic bacilli, 6 gram-neg. aerobic bacilli, and 10 gram-pos. aerobic cocci, isolated from the intestines of rabbits fed chenodeoxycholic acid (I) for long periods. Activity to deconjugate either or both of taurine- and glycine-conjugates of deoxycholic acid was demonstrated in 41 of the 52 strains. Seventy-nine percent of the gram-neg. anaerobic bacilli, all gram-pos. anaerobic bacilli, and most of the gram-pos. aerobic cocci were active for deconjugation. Twenty-four strains, including 67% of the gram-neg. anaerobic bacilli and all of the gram-neg. aerobic bacilli dehydrogenated the 7α-hydroxyl group of I and cholic acid (II). Four strains of gram-pos. anaerobic bacilli dehydrogenated the 3α-hydroxyl group, but to a much lesser extent. None of the strains dehydroxylated the 7α-hydroxyl group of I and II. Of 41 strains with deconjugating activity, 14 showed specificity to **bile acids**, 10 deconjugating only glycodeoxycholate with the remaining 4 being active only to taurodeoxycholate. The specificity depended on the amino acid moiety. All strains active for 7α-dehydrogenation dehydrogenated I and II in parallel. With gram-neg. aerobic bacilli, the rate of dehydrogenation was highest when incubated in air with shaking and lowest when incubated anaerobically in N2 atmosphere. Although the reaction between I and its oxidation product, 7-ketolithocholic acid (III), was reversible, no stereospecific reduction of III to **urodeoxycholic acid** was observed With gram-neg. aerobic bacilli, which had dehydrogenation activity but no deconjugation activity, 7α-dehydrogenation took place in the I-moiety in their conjugate without preceding deconjugation.

L19 ANSWER 10 OF 11 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
79083700 EMBASE Document No.: 1979083700. Changes in **bile acid** metabolism by administration of chenodeoxycholic acid and **urodeoxycholic acid.** Nakagawa S.; Makino I.. II Dept. Med., Hakkaido Univ. Sch. Med., Sapporo, Japan. Japanese Journal of Medicine Vol. 17, No. 1, pp. 67-68 1978.
CODEN: JJMDAT
Pub. Country: Japan. Language: English.
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L19 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
1970:423675 Document No. 73:23675 Measurement of the selective damage of cancer cells in vitro using attack combinations of hyperacidification, + 40.deg. hyperthermia, and various **bile acids** of favorable pH-dependence. Von Ardenne, Manfred; Reitnauer, Paul G. (Forschungsinst. Manfred Ardenne, Dresden, Fed. Rep. Ger.). Arzneimittel-Forschung, 20(3), 323-9 (German) 1970. CODEN: ARZNAD. ISSN: 0004-4172.

AB **Bile acids** (i.e. chenodeoxycholic acid, Na deoxycholate, deoxycholic acid, **urodeoxycholic acid**, cholic acid, glycodeoxycholic acid) elicited a strong cancerolytic activity on Ehrlich-mouse-ascites carcinomas at pH <6.7. These results, their toxicol. data, and their pharmacokinetic properties indicate that **bile acids** are well suited for initiating whole-body attack combined with the double attack of optimated tumor hyperacidity and 40°. Furthermore it was found that cancer cell antibodies are strongly charged with **bile acids.**

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=> s l7 and dehydrocholic acid
L20         669 L7 AND DEHYDROCHOLIC ACID

=> s l20 and humans
L21          41 L20 AND HUMANS

=> s l21 and inflammation
L22           0 L21 AND INFLAMMATION

=> s l21 and heart
L23           0 L21 AND HEART

=> dup remove l21
PROCESSING COMPLETED FOR L21
L24          32 DUP REMOVE L21 (9 DUPLICATES REMOVED)

=> d l24 1-32 cbib abs
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L24 ANSWER 1 OF 32 MEDLINE on STN
2004448422. PubMed ID: 15356194. Lasting blood-brain barrier disruption induces epileptic focus in the rat somatosensory cortex. Seiffert Ernst; Dreier Jens P; Ivens Sebastian; Bechmann Ingo; Tomkins Oren; Heinemann Uwe; Friedman Alon. (Johannes-Muller-Institute of Physiology, Charite, University Medicine, 10117 Berlin, Germany.) Journal of neuroscience : official journal of the Society for Neuroscience, (2004 Sep 8) 24 (36) 7829-36. Journal code: 8102140. ISSN: 1529-2401. Pub. country: United States. Language: English.

AB Perturbations in the integrity of the blood-brain barrier have been reported in both **humans** and animals under numerous pathological conditions. Although the blood-brain barrier prevents the penetration of many blood constituents into the brain extracellular space, the effect of such perturbations on the brain function and their roles in the pathogenesis of cortical diseases are unknown. In this study we established a model for focal disruption of the blood-brain barrier in the rat cortex by direct application of bile salts. Exposure of the cerebral cortex in vivo to bile salts resulted in long-lasting extravasation of serum albumin to the brain extracellular space and was associated with a prominent activation of astrocytes with no inflammatory response or marked cell loss. Using electrophysiological recordings in brain slices we found that a focus of epileptiform discharges developed within 4-7 d after treatment and could be recorded up to 49 d postoperatively in >60% of slices from treated animals but only rarely (10%) in sham-operated controls. Epileptiform activity involved both glutamatergic and GABAergic neurotransmission. Epileptiform activity was also induced by direct cortical application of native serum, denatured serum, or

albumin-containing solution. In contrast, perfusion with serum-adapted electrolyte solution did not induce abnormal activity, thereby suggesting that the exposure of the serum-devoid brain environment to serum proteins underlies epileptogenesis in the blood-brain barrier-disrupted cortex. Although many neuropathologies entail a compromised blood-brain barrier, this is the first direct evidence that it may have a role in the pathogenesis of focal cortical epilepsy, a common neurological disease.

L24 ANSWER 2 OF 32 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 1
2003:540036 Document No.: PREV200300542586. Feeding natural hydrophilic **bile acids** inhibits intestinal cholesterol absorption: Studies in the gallstone-susceptible mouse. Wang, David Q.-H. [Reprint Author]; Tazuma, Susumu; Cohen, David E.; Carey, Martin C.. Dept. of Medicine, Gastroenterology Division, Beth Israel Deaconess Medical Center, 330 Brookline Ave., DA 601, Boston, MA, 02215, USA. dqwang@caregroup.harvard.edu. American Journal of Physiology, (September 2003) Vol. 285, No. 3 Part 1, pp. G494-G502. print.
ISSN: 0002-9513 (ISSN print). Language: English.
AB We explored the influence of the hydrophilic-hydrophobic balance of a series of natural **bile acids** on cholesterol absorption in the mouse. Male C57L/J mice were fed standard chow or chow supplemented with 0.5% cholic; chenodeoxycholic; deoxycholic; dehydrocholic; hyocholic; hyodeoxycholic; alpha-, beta-, or omega-muricholic; ursocholic; or ursodeoxycholic acids for 7 days. Biliary bile salts were measured by reverse-phase HPLC, and hydrophobicity indices were estimated by Heuman's method. Cholesterol absorption efficiency was determined by a plasma dual-isotope ratio method. In mice fed chow, natural proportions of tauro-beta-muricholate (42+-6%) and taurocholate (50+-7%) with a hydrophobicity index of -0.35+-0.04 produced cholesterol absorption of 37+-5%. Because bacterial and especially hepatic biotransformations of specific **bile acids** occurred, hydrophobicity indices of the resultant bile salt pools differed from fed **bile acids.** We observed a significant positive correlation between hydrophobicity indices of the bile salt pool and percent cholesterol absorption. The principal mechanism whereby hydrophilic **bile acids** inhibit cholesterol absorption appears to be diminution of intraluminal micellar cholesterol solubilization. Gene expression of intestinal sterol efflux transporters Abcg5 and Abcg8 was upregulated by feeding cholic acid but not by hydrophilic beta-muricholic acid nor by hydrophobic deoxycholic acid. We conclude that the hydrophobicity of the bile salt pool predicts the effects of individual fed **bile acids** on intestinal cholesterol absorption. Natural alpha- and beta-muricholic acids are the most powerful inhibitors of cholesterol absorption in mice and might act as potent cholesterol-lowering agents for prevention of cholesterol deposition diseases in **humans.**

L24 ANSWER 3 OF 32 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
2003342116 EMBASE Feeding natural hydrophilic **bile acids** inhibits intestinal cholesterol absorption: Studies in the gallstone-susceptible mouse. Wang D.Q.-H.; Tazuma S.; Cohen D.E.; Carey M.C.. D.Q.-H. Wang, Dept. of Medicine, Gastroenterology Division, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA 02215, United States. dqwang@caregroup.harvard.edu. American Journal of Physiology - Gastrointestinal and Liver Physiology Vol. 285, No. 3 48-3, pp. G494-G502 1 Sep 2003.
Refs: 50.
ISSN: 0193-1857. CODEN: APGPDF
Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 20030911
AB We explored the influence of the hydrophilic-hydrophobic balance of a series of natural **bile acids** on cholesterol absorption in the mouse. Male C57L/ J mice were fed standard chow or chow

supplemented with 0.5% cholic; chenodeoxycholic; deoxycholic; dehydrocholic; hyocholic; hyodeoxycholic; α-, β-, or ω-muricholic; ursocholic; or ursodeoxycholic acids for 7 days. Biliary bile salts were measured by reverse-phase HPLC, and hydrophobicity indices were estimated by Heuman's method. Cholesterol absorption efficiency was determined by a plasma dual-isotope ratio method. In mice fed chow, natural proportions of tauro-β-muricholate (42 ± 6%) and taurocholate (50 ± 7%) with a hydrophobicity index of -0.35 ± 0.04 produced cholesterol absorption of 37 ± 5%. Because bacterial and especially hepatic biotransformations of specific **bile acids** occurred, hydrophobicity indices of the resultant bile salt pools differed from fed **bile acids.** We observed a significant positive correlation between hydrophobicity indices of the bile salt pool and percent cholesterol absorption. The principal mechanism whereby hydrophilic **bile acids** inhibit cholesterol absorption appears to be diminution of intraluminal micellar cholesterol solubilization. Gene expression of intestinal sterol efflux transporters Abcg5 and Abcg8 was upregulated by feeding cholic acid but not by hydrophilic β-muricholic acid nor by hydrophobic deoxycholic acid. We conclude that the hydrophobicity of the bile salt pool predicts the effects of individual fed **bile acids** on intestinal cholesterol absorption. Natural α- and β-muricholic acids are the most powerful inhibitors of cholesterol absorption in mice and might act as potent cholesterol-lowering agents for prevention of cholesterol deposition diseases in **humans.**

L24 ANSWER 4 OF 32 MEDLINE on STN

2002400647. PubMed ID: 12057645. **Bile acid** derivatives of 5-amino-1,3,4-thiadiazole-2-sulfonamide as new carbonic anhydrase inhibitors: synthesis and investigation of inhibition effects. Bulbul Metin; Saracoglu Nurullah; Kufrevioglu O Irfan; Ciftci Mehmet. (Faculty of Science and Arts, Department of Chemistry, Ataturk University, 25240 Erzurum, Turkey.) Bioorganic & medicinal chemistry, (2002 Aug) 10 (8) 2561-7. Journal code: 9413298. ISSN: 0968-0896. Pub. country: England: United Kingdom. Language: English.

AB **Bile acid** amides (cholan-24-amides) of 5-substituted 1,3,4-thiadiazole-2-sulfonamide have been prepared from lithocholic, deoxycholic, cholic and **dehydrocholic acids.** Besides, the alcohol functional groups on the cholane ring systems were protected with acetyl group. Amides of the protected cholanes of lithocholic and cholic acids were also synthesized. Later, inhibition effects of these compounds on human carbonic anhydrase isozymes (HCA-I and II) have been investigated in vitro. For the most active compounds, inhibition constants ranged from 66 to 190nM for HCA-II with I(50) (molarity of inhibitor producing a 50% inhibition of CA activity). In addition, in vivo studies were performed for the synthesized compounds in Sprague-Dawley rats. The compounds (11 and 18) showed especially significant inhibition efficacy ($p<0.001$).

L24 ANSWER 5 OF 32 MEDLINE on STN

2000286789. PubMed ID: 10827473. [Role of **bile acids** and endotoxins in the pathogenesis and therapy of psoriasis]. Epesavak es endotoxinok szerepe a pikkelysomor korfejlodeseben es kezeleseben. Gyurcsovics K; Bertok L. (Petz Aladar Megyei Korhaz, Gyor.) Orvosi hetilap, (2000 Apr 23) 141 (17) 915-7. Journal code: 0376412. ISSN: 0030-6002. Pub. country: Hungary. Language: Hungarian.

AB The authors demonstrated significant curative effect of **bile acids** (Suprachol; Acidum dehydrocholicum) in 551 psoriatic patients. The clinical efficiancy was evaluated by means of PASI-score (Psoriasis Area Severity Index). During this treatment (1-8 weeks) 434 patients (78.8 per cent) became asymptomatic. However, the traditional therapy resulted in 62 patients (24.9 per cent) of 249 sick persons a recovery ($p < 0.05$). In acute form of psoriasis (184 patients) this curative effect of **bile acids** was elevated (95.1 per cent). Two years later 319 patients (57.9 per cent) of bile treated 551

people were asymptomatic in contrast with 15 people (6.0 per cent) of 249 traditional treated patients ($p < 0.05$). In same time among the patients which were treated in acute form of psoriasis 10 (7.2 per cent) of 139 controls and 147 (79.9 per cent) of 184 bile-treated individuals were asymptomatic ($p < 0.01$). On the basis of their clinical observations (digestive disorders, ultrasonical confirmed gallbladder complaints, etc.) authors supposed that the deficiency of **bile acids** and the consecutive endotoxin translocation might play a role in the pathogenesis of psoriasis. In normal conditions the **bile acids** as detergent (physico-chemical defense) can protect the body against enteral endotoxins while split them to atoxic fragments and so preventing consecutive cytokin liberation.

L24 ANSWER 6 OF 32 MEDLINE on STN
96434315. PubMed ID: 8837294. A novel enzyme system for the reduction of 3-oxo **bile acids** in human red blood cells. Goto J; Miura H; Ando M; Yamato Y; Ikegawa S; Nambara T; Makino I. (Faculty of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai, Japan.) Steroids, (1996 Jul) 61 (7) 416-20. Journal code: 0404536. ISSN: 0039-128X. Pub. country: United States. Language: English.

AB 7 alpha,12 alpha-Dihydroxy-3-oxo- and 3,7,12-trioxo-5 beta-cholanoic acids labeled with 18O atoms were incubated with human red blood cells, and the biotransformation products were separated and characterized by gas chromatography-mass spectrometry as the pentafluorobenzyl ester-trimethylsilyl and -dimethylethylsilyl ether derivatives with the negative ion chemical ionization mode. The reduced products, 3 beta,7 alpha,12 alpha-trihydroxy-5 beta-cholanoic acid for the former, and 3 alpha-hydroxylated dioxo **bile acid** together with 3 beta-hydroxylated 7,12-dioxo-5 beta-cholanoic acid for the latter, were identified as metabolites. When 3-oxo **bile acid** was incubated with human blood denatured at 70 degrees C for 2 min, no metabolites were formed. The enzymic reduction activity has been localized in the red blood cell fraction.

L24 ANSWER 7 OF 32 MEDLINE on STN
95093587. PubMed ID: 8000511. Identification and characterization of **dehydrocholic acid** reductase system in the cytosol of human red blood cells. Tani M; Goto J; Makino I. (Second Department of Internal Medicine, Asahikawa Medical College, Japan.) Journal of gastroenterology, (1994 Oct) 29 (5) 621-30. Journal code: 9430794. ISSN: 0944-1174. Pub. country: Japan. Language: English.

AB We conducted in vivo and in vitro studies of the reductive metabolism of the cholagogue, **dehydrocholic acid** (DHCA). Immediately after the intravenous administration of 1 g of DHCA in normal subjects (n = 6), the concentration of the reductive metabolite, 3 alpha-hydroxy-7,12-dioxo-cholanoic acid (unconjugated form), increased sharply in the systemic circulation, rising to 95.8 microM 10 min after administration. The results of in vitro experiments with DHCA and whole blood showed that 3 alpha-hydroxy-7,12-dioxocholanoic acid were produced from DHCA. In vitro experiments using DHCA and the red blood cell fraction, and DHCA and the red blood cell cytoplasmic fraction gave similar results to those described above with whole blood. However, a reductive metabolite was not formed by the incubation of DHCA and the red blood cell membrane fraction. These findings indicated that, contrary to the conventional theory that intravenously administered DHCA is subjected to reductive metabolism only in the liver, reduction also occurs in the systemic circulation, and the mechanism for this reductive metabolism is present in the cytoplasmic fraction of red blood cells. Further investigation to characterize this reductive metabolic system revealed an optimum temperature of 37 degrees C, an optimum pH of 7.4, a Km value of 2.0 x 10(-3) M, and inactivation by heat treatment (70 degrees C for 2 min).

L24 ANSWER 8 OF 32 MEDLINE on STN DUPLICATE 2
93292015. PubMed ID: 8513444. Potentiation of butyrate-induced

differentiation in human colon tumor cells by deoxycholate. Desai T K; Nathan D F; Morin M J. (Section of Gastroenterology, Northwestern University Medical School, Chicago, IL 60611.) Cancer letters, (1993 May 14) 69 (3) 181-6. Journal code: 7600053. ISSN: 0304-3835. Pub. country: Netherlands. Language: English.

AB Human colon adenocarcinoma cells, treated with deoxycholate for 24 h prior to exposure to 1 mM butyrate, exhibited dose-dependent increases in the activities of three markers of colonic differentiation (alkaline phosphatase, lactase and CEA). Treatment with deoxycholate alone, for 24 h or longer, did not increase the secretion of CEA or the activities of either of the brush border-associated enzyme activities. Increases in differentiation markers were found to be **bile acid** -specific. Pretreatment with either **dehydrocholic acid** or cholic acid, even at cytotoxic concentrations, led to no significant butyrate-induced increases in brush-border associated hydrolase activities. The addition of a bacterial superoxide dismutase decreased the short-term cytotoxicity of deoxycholate and increased the maturation-potentiating effects of the **bile acid** in HCT-116 DO cells. The results of these studies demonstrate that **bile acids**, which are commonly thought to have tumor promoting activities in vivo, may also have physiological effects which serve to limit carcinogenic processes in the human colon by potentiating tumor cell differentiation.

L24 ANSWER 9 OF 32 MEDLINE on STN

94063125. PubMed ID: 8243708. [The role of **bile acids** in the regulation of human gallbladder filling]. Rol zhovchnykh kyslot u reguliatsii napovnennia zhovchnogo mikhura liudyny. Berezovskyi V A; Nykula T D; Dynnyk O B; Pavlyk I V; Korychenskyi O M. Fiziologicheskii zhurnal, (1993 Jul-Aug) 39 (4) 103-7. Journal code: 7806822. ISSN: 0201-8489. Pub. country: RUSSIA: Russian Federation. Language: Ukrainian.

AB An artificial increase of a pool of **bile acids** due to administration of dehydrocholic, chenodesoxycholic acid preparations and dry bile in 22 healthy people and 179 patients with chronic cholecystitis has been studied for its effect on regulation of the gallbladder filling on an empty stomach using daily echocholecystometry. Filling of the gallbladder under artificial sequestration of **bile acids** during duodenal probing, enterosorption and cholatogenic diarrhea was studied in 55 patients with cholecystitis. It has been proved that an increase of the pool of **bile acids** induces intensification of the gallbladder filling on an empty stomach, while a decrease of the pool, vice versa, causes attenuation of its filling. It is found out a size of a pool of **bile acids** in the human organism is an important humoral factor in the physiological mechanism of the gallbladder filling regulation.

L24 ANSWER 10 OF 32 MEDLINE on STN DUPLICATE 3

90275178. PubMed ID: 2350530. The effect of food and **bile acid** administration on the relative bioavailability of cyclosporin. Lindholm A; Henricsson S; Dahlqvist R. (Department of Clinical Pharmacology, Huddinge Hospital, Sweden.) British journal of clinical pharmacology, (1990 May) 29 (5) 541-8. Journal code: 7503323. ISSN: 0306-5251. Pub. country: ENGLAND: United Kingdom. Language: English.

AB 1. The relative bioavailability of cyclosporin was studied in 11 healthy volunteers after single oral capsule doses of cyclosporin on three separate occasions; fasting, with breakfast and with breakfast together with **bile acid** tablets (400 mg of cholic acid and 100 mg of **dehydrocholic acid**). 2. There was a significant increase in the area under the blood concentration vs time curve (AUC) of cyclosporin when the drug was taken together with breakfast and **bile acid** tablets (9078 ng ml-1 h) as compared with breakfast alone (7453 ng ml-1 h, P less than 0.05) or fasting conditions (7283 ng ml-1 h, P less than 0.01). 3. A blood drug concentration vs time curve displaying two peaks was present in 9/11 subjects when cyclosporin was taken with breakfast or with breakfast and **bile acid**

tablets, but only one peak was present when cyclosporin was taken during fasting, suggesting an enterohepatic circulation of cyclosporin or a second absorption phase after the meal. 4. In a separate study, 12 h trough blood cyclosporin concentrations were measured before and after 1 week of **bile acid** treatment in 19 clinically stable, out-patient transplant recipients who were treated with oral cyclosporin solution (mean dose 2.0 mg kg-1 twice daily). The administration of cyclosporin was not standardized with regard to food intake. There was no significant difference in the blood concentrations of cyclosporin before and after **bile acid** treatment (114 +/- 38 ng ml-1 vs 121 +/- 38 ng ml-1).(ABSTRACT TRUNCATED AT 250 WORDS)

L24 ANSWER 11 OF 32 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

1989:430046 Document No.: PREV198988088304; BA88:88304. REDUCTIVE BIOTRANSFORMATION OF 3 OXO **BILE ACIDS** IN HUMAN BLOOD.
GOTO J [Reprint author]; MIURA H; ANDO M; NAMBARA T; MAKINO I. PHARM INST, TOHOKU UNIV, AOBAYAMA, SENDAI 980, JPN. Chemical and Pharmaceutical Bulletin (Tokyo), (1989) Vol. 37, No. 7, pp. 1960-1962.
CODEN: CPBTAL. ISSN: 0009-2363. Language: ENGLISH.

AB 7α,12α-Dihydroxy-3-oxo-5β-cholanoic acid labeled with 18O atoms was incubated with human blood, and the biotransformation products were separated and characterized by gas chromatography-mass spectrometry as the pentafluorobenzyl ester-trimethylsilyl and -dimethylethylsilyl ether derivatives. 3β,7α,12α-Trihydroxy-5β-cholanoic acid was identified as a main metabolite. When 3-oxo **bile acid** was incubated with human blood denatured at 70°C for 2 min, no metabolites were formed. The enzymic reduction activity proved to be localized in the red blood cell fraction.

L24 ANSWER 12 OF 32 MEDLINE on STN

89148171. PubMed ID: 2919585. The biotransformed metabolite profiles in blood after intravenous administration of **dehydrocholic acid.** Yoneda M; Makino I; Tamasawa N; Takebe K; Sakuraba K; Goto J; Nambara T. (Third Department of Internal Medicine, Hirosaki University School of Medicine, Japan.) American journal of gastroenterology, (1989 Mar) 84 (3) 290-5. Journal code: 0421030. ISSN: 0002-9270. Pub. country: United States. Language: English.

AB One gram of **dehydrocholic acid** was injected intravenously into two patients with percutaneous transhepatic cholangial drainage, and the biotransformed metabolites profiles over a 120-min period in serum and bile were analyzed. In serum unconjugated 3 alpha-hydroxy-7,12-dioxo-cholanoic acid (3 alpha-OH-7,12-OXO) acid was markedly increased after the injection of **dehydrocholic acid**, and reached about 80 microM within 30 min. On the other hand, conjugated 3 alpha, 7 alpha-dihydroxy-12-oxo-cholanoic acid (3 alpha,7 alpha-OH-12-OXO) was consecutively increased with lag time to an elevation of 3 alpha-OH-7,12-OXO. In bile, the major constituent of metabolites was conjugated 3 alpha,7 alpha-OH-12-OXO (more than 90% of the excreted metabolites), while conjugated 3 alpha-OH-7,12-OXO was detected as minor constituent. Therefore, between bile and serum, there was great difference in biotransformed metabolites profiles. The mechanism of elevation of unconjugated 3 alpha-OH-7,12-OXO in serum remains obscure, but this new finding raised a question as to whether organ-reducing 3-keto group of **dehydrocholic acid** is restricted to the liver.

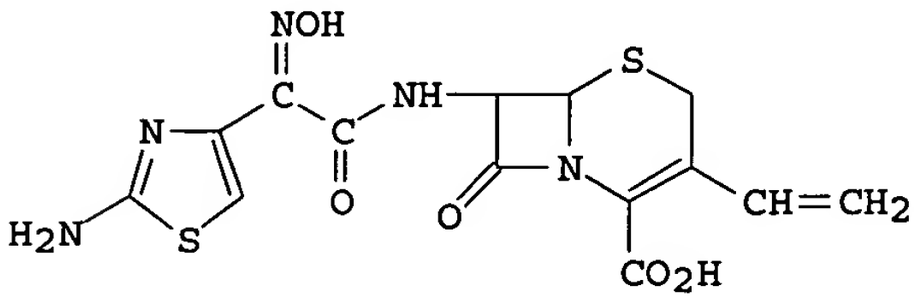
L24 ANSWER 13 OF 32 MEDLINE on STN DUPLICATE 4

88301193. PubMed ID: 3404755. Development of enzymatic determination of 3-keto **bile acids** in serum. Yoneda M; Tamasawa N; Makino I; Takebe K. Nippon Shokakibyo Gakkai zasshi The Japanese journal of gastro-enterology, (1988 Apr) 85 (4) 904-9. Journal code: 2984683R. ISSN: 0446-6586. Pub. country: Japan. Language: Japanese.

L24 ANSWER 14 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN

1988:226860 Document No. 108:226860 Oral formulaltions containing FR 80482 Substance (an antibiotic) and absorption accelerators. Ueda, Yoshio; Shimojo, Fumio; Miyatake, Toshiko; Ozaki, Midori (Fujisawa Pharmaceutical Co., Ltd., Japan). Jpn. Kokai Tokkyo Koho JP 62265226 A2 19871118 Showa, 4 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1986-108283 19860512.

GI



I

AB Free amino acids or their salts, **bile acids** or their salts, and sucrose fatty acid esters are accelerators of absorption of FR 80482 Substance (I, an antibiotic) administered orally to **humans** . NaHCO3 (0.5%, 2.5 mL) was added to I (50 mg titer) and glycine (50 mg) to give an antibiotic solution

L24 ANSWER 15 OF 32 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

1987:387245 Document No.: PREV198733067385; BR33:67385. DETECTION OF THE REDUCED **DEHYDROCHOLIC ACID** IN SERUM FOLLOWING ADMINISTRATION OF **DEHYDROCHOLIC ACID** AND ITS METABOLISM IN NORMAL SUBJECTS. TAMASAWA N [Reprint author]; ET AL. THIRD DEP MED, HIROSAKI UNIV SCH MED, HIROSAKI, JPN. Japanese Journal of Gastroenterology, (1987) Vol. 84, No. 4, pp. 948. ISSN: 0446-6586. Language: JAPANESE.

L24 ANSWER 16 OF 32 MEDLINE on STN DUPLICATE 5

86223942. PubMed ID: 3458705. 3 beta-Hydroxysteroid dehydrogenase of Ruminococcus sp. from human intestinal bacteria. Akao T; Akao T; Hattori M; Namba T; Kobashi K. Journal of biochemistry, (1986 May) 99 (5) 1425-31. Journal code: 0376600. ISSN: 0021-924X. Pub. country: Japan. Language: English.

AB Ruminococcus sp. PO1-3 obtained from human intestinal flora is able to reduce dehydrocholate as well as 3-ketoglycyrrhetinate. From this bacterium dehydrocholate- and 3-ketoglycyrrhetinate-reducing activities were purified one thousand-fold together with 3-ketocholanate-reducing and 3-beta-hydroxyglycyrrhetinate (glycyrrhetic acid) oxidizing activities by means of Matrex Red A, Sephadex G-200 and Octyl-Sepharose column chromatography. The purified enzyme catalyzed the reduction of **dehydrocholic acid** to 3 beta-hydroxy-7,12-diketocholanic acid and of 3-ketocholanic acid to 3 beta-hydroxycholanic acid. Studies on substrate specificity revealed that the enzyme had absolute specificity for the beta-configuration of a hydroxyl group at the 3 position of **bile acid** and steroids having no double bond in the A/B ring. This enzyme was neither beta-hydroxysteroid dehydrogenase [EC 1.1.1.51] nor 3 beta-hydroxy-delta 5-steroid dehydrogenase [EC 1.1.1.145], but a novel type of enzyme, defined as 3 beta-hydroxysteroid dehydrogenase.

L24 ANSWER 17 OF 32 MEDLINE on STN

86219857. PubMed ID: 2872047. The effect of drugs on bile flow and composition. An overview. Okolicsanyi L; Lirussi F; Strazzabosco M; Jemmolo R M; Orlando R; Nassuato G; Muraca M; Crepaldi G. Drugs, (1986 May) 31 (5) 430-48. Ref: 165. Journal code: 7600076. ISSN: 0012-6667. Pub. country: Australia. Language: English.

AB Many drugs are eliminated via the hepatobiliary route, after biotransformation in the liver. Some of them may affect bile flow and/or

the hepatic secretion of biliary lipids such as **bile acids**, cholesterol and phospholipids. **Bile acids** are the most potent agents which increase bile flow, especially unconjugated **bile acids.** Other drugs which increase bile flow include phenobarbitone (phenobarbital), theophylline, glucagon and insulin. In contrast, ethacrynic acid, amiloride, ouabain, oestrogens and chlorpromazine are among those agents which decrease bile flow. Biliary **bile acid** secretion is altered by a variety of drugs, including cheno- and ursodeoxycholic acids (CDCA and UCDA), the **bile acid** sequestrants cholestyramine and colestipol, and ethinyloestradiol. The composition of bile can also be altered by drug therapy. Thus, clofibrate increases biliary cholesterol secretion, and reduces **bile acid** concentrations, without altering biliary phospholipid concentrations. However, other clofibrate derivatives may produce changes of a different pattern, suggesting that the risk of developing gallstones may differ for each derivative. Nicotinic acid and d-thyroxine also increase biliary cholesterol saturation, while CDCA and UDCA reduce biliary cholesterol concentration. The potential consequences of drug-induced changes in bile flow and composition extend to the liver, the gallbladder and the intestine. If adverse effects are to be avoided, further study in this often overlooked area is required.

L24 ANSWER 18 OF 32 MEDLINE on STN

86208864. PubMed ID: 3704950. [Gas chromatographic determination of serum **bile acid** levels in chronic cholecystitis patients]. Gazokhromatograficheskoe opredelenie soderzhaniia zhelchnykh kislot syvorotki krovi u bol'nykh khronicheskim kholetsistitom. Mansurov Kh Kh; Orziev Z M. Terapevticheskii arkhiv, (1986) 58 (2) 96-100. Journal code: 2984818R. ISSN: 0040-3660. Pub. country: USSR. Language: Russian.

AB Serum **bile acids** were studied in 27 patients with chronic noncalculous cholecystitis. It was ascertained that the total concentration of **bile acids** under study was appreciably increased as compared with the data derived in the control group patients. There was noticeable differences between modulations in individual fractions of serum **bile acids**, attesting to an unusual distress of the synthetic function of hepatocytes. Alterations in the metabolism of cholates seen in chronic cholecystitis agreed well with the pattern of the disordered motor function of the gallbladder and were more pronounced in patients with hypokinesia.

L24 ANSWER 19 OF 32 MEDLINE on STN DUPLICATE 6

85119189. PubMed ID: 3969982. Hepatobiliary scintigraphy for cholestasis in congenital hepatic fibrosis. Diagnosis and treatment. Stillman A E; Earnest D L; Woolfenden J M. American journal of diseases of children (1960), (1985 Jan) 139 (1) 41-5. Journal code: 0370471. ISSN: 0002-922X. Pub. country: United States. Language: English.

AB A 9-year-old child with congenital hepatic fibrosis had dilated intrahepatic bile ducts and recurrent cholangitis. Choleretic agents were administered to prevent recurrent cholangitis. Response to treatment was monitored with serum **bile acid** concentrations and computer-assisted technetium Tc 99m iprofenin (Pipida) scintigraphy. **Dehydrocholic acid** with meals improved hepatobiliary excretion of the radioactive isotope and lowered serum **bile acid** levels but did not prevent cholangitic attacks when used alone. Sulfamethoxazole and trimethoprim used alone prevented infection, but a steady rise in serum **bile acid** concentrations suggested increasing cholestasis. During combined drug treatment, the patient remained free of cholangitis for at least two years. Optimal therapy of congenital hepatic fibrosis with cholestasis but without mechanical biliary obstruction may involve the combined use of a choleretic such as **dehydrocholic acid** plus a suppressive antibiotic.

L24 ANSWER 20 OF 32 MEDLINE on STN

84030423. PubMed ID: 6629304. Intravenous dehydrocholate tolerance test in patients with liver disease. Wakushima T; Kishimoto Y; Hirayama C. Hepato-gastroenterology, (1983 Aug) 30 (4) 137-9. Journal code: 8007849. ISSN: 0172-6390. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB The disappearance of intravenously administered dehydrocholate was studied in 13 healthy subjects and 23 patients with chronic liver disease. Serum dehydrocholate was determined by the enzymatic method using 3 alpha-hydroxysteroid dehydrogenase. Following the loading dose of dehydrocholate, serum dehydrocholate and 3 alpha-hydroxy **bile acid** were assayed at five minute intervals for 15 minutes. During this 15 minute period, dehydrocholate decreased and 3 alpha-hydroxy **bile acid** increased. The disappearance of the dehydrocholate was delayed in patients with chronic liver disease, and the 5-minute retention value was significantly high in cirrhosis patients.

L24 ANSWER 21 OF 32 MEDLINE on STN

82166737. PubMed ID: 7068349. Impairment of bromosulfophthalein clearance by bile salt administration in normal volunteers and patients with Dubin-Johnson syndrome. Bar-Meir S; Levy R; Halperin Z; Levy-Gigi C; Gilat T. Israel journal of medical sciences, (1982 Feb) 18 (2) 211-4. Journal code: 0013105. ISSN: 0021-2180. Pub. country: Israel. Language: English.

AB Sodium dehydrocholate administration significantly impaired bromosulfophthalein (BSP) clearance in six normal volunteers, despite its choleretic effect. In order to determine whether the impairment is at the stage of excretion of BSP from the liver cell into the bile, patients with Dubin-Johnson syndrome were studied. In all six Dubin-Johnson patients, sodium dehydrocholate administration significantly decreased BSP clearance. Since serum **bile acid** levels are normal in Dubin-Johnson patients, presumably due to a final secretory pathway into the bile distinct from that of BSP and other organic anions, the interaction between BSP and **bile acids** cannot take place at the stage of excretion into the bile. Based on a previous study and our results, the interaction between BSP and bile salts seems to occur at the site of transport within the liver cell. This mechanism of inhibition may be responsible for the increased serum BSP retention during chemotherapy.

L24 ANSWER 22 OF 32 MEDLINE on STN DUPLICATE 7

80135053. PubMed ID: 535692. [Hepatic biotransformation and conjugation of **dehydrocholic acid** in patients with cirrhosis (author's transl)]. Biotransformation et conjugaison hepatiques de l'acide dehydrocholique au cours des cirrhoses. Poupon R Y; Raizman A; Brumault J C; Infante R; Darnis F. Gastroenterologie clinique et biologique, (1979 Dec) 3 (12) 879-84. Journal code: 7704825. ISSN: 0399-8320. Pub. country: France. Language: French.

L24 ANSWER 23 OF 32 MEDLINE on STN

81058832. PubMed ID: 552771. [The clinical significance of radioimmunologically determined serum **bile acids** as a new liver function test and the development of a new intravenous sulfolithoglycocholic acid (SLGC) stimulation test]. Die klinische Bedeutung radioimmunologisch bestimmter Serumgallensauren als neuer Leberfunktionstest und die Entwicklung eines neuen intravenosen Sulfolithoglykocholsaure-(SLCG-) Stimulationstests. Biffl H; Goebel R; Leb G. Acta medica Austriaca, (1979) 6 (4) 113-20. Journal code: 7501997. ISSN: 0303-8173. Pub. country: Austria. Language: German.

AB Cholylglycin (CG-) and SLCG levels were measured in patients with various biopsy-confirmed liver and bile disease. SLCG values were found to be more sensitive, and to distinguish clearly between steatosis hepatis and normals, as well as between cirrhosis hepatis, with and without, portal hypertension. Correlations between the common liver tests and the SLCG levels were poor, but a clear distinction was possible between the various histologically defined liver diseases. The paper concludes with a description of a new method of stimulating the SLCG values, intravenously.

Using this method, it is possible to keep consumption of material and time and incommodities inflicted to the patient, as low as possible. Nevertheless staging of parenchymatous liver diseases, is feasible.

L24 ANSWER 24 OF 32 MEDLINE on STN
79030902. PubMed ID: 568204. The dual effect of glycocholate on hepatic dihydroxy **bile acid** excretion. Sarfeh I J; Friday S E; Balint J A. Journal of surgical research, (1978 Sep) 25 (3) 280-7. Journal code: 0376340. ISSN: 0022-4804. Pub. country: United States. Language: English.

L24 ANSWER 25 OF 32 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
1978:140605 Document No.: PREV197865027605; BA65:27605. BACTERIOSTATIC AND BACTERICIDAL EFFECT OF **BILE ACIDS** ON STAPHYLOCOCCI.
ANDREICHYN M A [Reprint author]; SYTNYK I O. TERNOP MED INST, TERNOPOL, USSR. Mikrobiolohichnyi Zhurnal (Kiev), (1977) Vol. 39, No. 2, pp. 185-187.
CODEN: MZUKAV. ISSN: 0026-3664. Language: UKRAINIAN.
AB The antibacterial action of cholic, desoxycholic, glycocholic, choleic and **dehydrocholic acids** was studied on 45 strains of staphylococci isolated from bile of the patients with viral hepatitis and to 15 museum cultures. Desoxycholic acid manifested the highest bacteriostatic and bactericidal activity. **Dehydrocholic acid** had no essential effect on growth and reproduction of the bacteria. A higher resistance to some **bile acids** is established for staphylococci inoculated from bile. This should be taken into account when developing problems of pathogenesis and a method for treating the bacterial infections of the hepatobiliary system.

L24 ANSWER 26 OF 32 MEDLINE on STN
77017768. PubMed ID: 969779. [Effect of some choleretics on the hepatic flow and its composition in man]. Einfluss einiger Choleretika auf Volumen und Inhaltsstoffe der Galle beim Maenschen. Eulenburg F; Bode C. Zeitschrift fur Gastroenterologie, (1976 May) 14 (3) 354-64. Journal code: 0033370. ISSN: 0044-2771. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: German.
AB Four choleretics, selected at random from the German list of medical preparations, were tested with regards to their influence on hepatic bile production and bile composition. The investigations were performed on patients with a T-drainage in the ductus choledochus after bile duct revision. Bile was collected after fasting (90 min) and after administration of the drugs to be tested (3 hours). The choleretics were administered orally in a dosage two to five times more than the recommended one. Besides the bile volume **bile acids**, cholesterol, bilirubin, bicarbonate, potassium, sodium and calcium were determined. None of the parameters could be definitely influenced by these drugs. On the other hand a pronounced increase in the bile flow as well as the expected change in the other parameters could be observed after standardized secretion-stimulation which had been additionally carried out in half of the patients (**dehydrocholic acid**, i.v., taurocholic acid intraduodenally, secretin i.v., meals).

L24 ANSWER 27 OF 32 MEDLINE on STN
76013951. PubMed ID: 1099718. [Choleresis, choleretics and motility of the bile ducts]. Cholerese, Choleretika und Motilitat der Gallenwege. Bode J C. Tijdschrift voor gastro-enterologie, (1975) 18 (1) 35-48. Ref: 13. Journal code: 0404414. ISSN: 0049-3899. Pub. country: Belgium. Language: German.

L24 ANSWER 28 OF 32 MEDLINE on STN
74268493. PubMed ID: 4840818. Studies on bile secretion in man. 3. Influence of sodium dehydrocholate, a diuretic and glucagon on bile secretion. Kuska J. Archivum immunologiae et therapiae experimentalis, (1974) 22 (2) 207-35. Journal code: 0114365. ISSN: 0004-069X. Pub.

country: Poland. Language: English.

L24 ANSWER 29 OF 32 MEDLINE on STN
73242093. PubMed ID: 4666241. [Metabolism of **dehydrocholic acid**. Chromatographic study of its derivatives in the bile. "In vitro" study of their ability to form mixed micelles]. Metabolisme de l'acide dehydrocholique. Etude chromatographique de ses derives dans la bile. Etude "in vitro" de leur capacite a former des micelles mixtes. Gerolami A; Crotte C; Montet J C; Vigne J L; Granger M; Mule A. Biologie et gastro-enterologie, (1972) 5 (4) 265-72. Journal code: 0146364. ISSN: 0006-3258. Pub. country: France. Language: French.

L24 ANSWER 30 OF 32 MEDLINE on STN
72095658. PubMed ID: 5171795. [Measurement of choleretic effects in man]. Beitrag zum Problem der Objektivierung choleretischer Wirkungen beim Menschen. Maurer C. Arzneimittel-Forschung, (1971 Sep) 21 (9) 1375-9. Journal code: 0372660. ISSN: 0004-4172. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: German.

L24 ANSWER 31 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
1972:138475 Document No. 76:138475 Forty years study of **bile acids**. Yamasaki, Kazumi (Biochem. Inst., Univ. Tottori, Yonago, Japan). Yonago Acta Medica, 15(3), 171-87 (German) 1971. CODEN: YOAMAQ. ISSN: 0513-5710.
AB Results of chemical as well as biochem. studies of **bile acids** during the past 40 years are reviewed. Chemical dehydration reactions of **bile acids** in relation to Hammarsten's test of cholic acid; metabolism of **dehydrocholic acid** in exptl. animals including **humans**; biogenesis of bile salts, especially a new biogenetic pathway of chenodeoxycholic acid proposed by the author; and the future prospects of biol. and clin. developments in this field are discussed. 3 refs.

L24 ANSWER 32 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
1960:8184 Document No. 54:8184 Original Reference No. 54:1722h-i,1723a The decreasing effect of deoxycholic acid on blood cholesterol level of rats and **humans**. Yamasaki, Kazumi; Shimizu, Kyutaro; Yasumizu, Makoto; Sugihara, Tetsuhiko (Tottori Univ. Med. School, Yonago). Journal of Biochemistry (Tokyo, Japan), 46, 807-8 (Unavailable) 1959. CODEN: JOBIAO. ISSN: 0021-924X.
AB Continued oral administration of deoxycholic (I) or apocholic acid to rats (10 mg./day) resulted in a decrease of cholesterol in plasma and liver by about 20% in 5-10 days. There occurred no histopathol. changes in the organs. Cholic and **dehydrocholic acids** tended to increase the cholesterol levels. I (0.6 g. daily for 8 days) lowered plasma cholesterol of human subjects.

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=> s l7 and cholic acid
L25       12206 L7 AND CHOLIC ACID

=> s l25 and treatment
L26        1543 L25 AND TREATMENT

=> s l26 and heart
L27          35 L26 AND HEART

=> dup remove l27
PROCESSING COMPLETED FOR L27
L28           19 DUP REMOVE L27 (16 DUPLICATES REMOVED)

=> d l28 1-19 cbib abs

L28  ANSWER 1 OF 19  CAPLUS  COPYRIGHT 2005 ACS on STN
2005:1102591  Agents for improvement of nutrition, digestive tract, and muscle,
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and **treatment** of depression, menopausal syndrome, Alzheimer's disease, and inflammation, etc., containing natural specified products. Ochiai, Akio; Oosa, Takao (Onaga Kikaku Y. K., Japan). Jpn. Kokai Tokkyo Koho JP 2005281278 A2 20051013, 19 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2004-102216 20040331.

AB The invention provides agents for improvement of nutrition, digestive tract, and muscle, and **treatment** and/or prevention of depression, menopausal syndrome, Alzheimer's disease, inflammation, post-cerebral infarctional symptoms, motor paralysis, asthma, visual degradation, hepatitis, inflammatory intestinal disease, intestinal disfunction, **heart** disorder, liver disorder, renal disorder, diarrhea, and dementia, containing bile powders, bile exts., **bile acid**, bezoar, artificial bezoar, **cholic acid**, scymnol, scymnol esters, isoflavones, isoflavone glycosides, pungent substances, bitter substances, sour substances, vitamins, specified fatty acids, and/or specified other plant drugs. For example, a soft capsule containing curcumin 45, **cholic acid** 60, bezoar powder 100, soybean isoflavone glycoside 125, beeswax 55, and edible oil q.s. to 1200 mg was formulated.

L28 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

2004:717800 Document No. 141:200195 Secondary **bile acid** formation inhibitors containing α-galactosyl oligosaccharides, their uses, and inhibition of conversion of primary **bile acids** to secondary **bile acids** using the oligosaccharides. Yokota, Atsushi; Ishizuka, Satoshi; Asano, Ikuzo; Tomita, Fusao; Senba, Yoshihiro; Sakurai, Hiroaki (Hokkaido Tlo Co., Ltd., Japan; Nippon Beet Sugar Mfg. Co., Ltd.). Jpn. Kokai Tokkyo Koho JP 2004244365 A2 20040902, 14 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2003-35621 20030213.

AB Claimed are secondary **bile acid** formation inhibitors, carcinogenesis and/or cardiac disease prevention agents, lactic acid bacteria growth promoters, and triglyceride formation inhibitors containing α-galactosyl oligosaccharides. Thus, addition of raffinose to cholesterol-rich diet suppressed conversion of chenodeoxycholic acid to deoxycholic acid and increased count of Lactobacilli in cecal content in rats.

L28 ANSWER 3 OF 19 MEDLINE on STN DUPLICATE 1

2004098011. PubMed ID: 14988826. **Cholic acid** supplementation enhances cholesterol absorption in humans. Woollett Laura A; Buckley Donna D; Yao Lihang; Jones Peter J H; Granholm Norman A; Tolley Elizabeth A; Tso Patrick; Heubi James E. (Department of Pathology and Laboratory Medicine, University of Cincinnati College of Medicine, Ohio, USA.) Gastroenterology, (2004 Mar) 126 (3) 724-31. Journal code: 0374630. ISSN: 0016-5085. Pub. country: United States. Language: English.

AB BACKGROUND & AIMS: Qualitative and quantitative changes in intralumenal **bile acid** composition may alter cholesterol absorption and synthesis and low-density lipoprotein (LDL) receptor expression. The role of **cholic acid** (CA) in cholesterol absorption in humans remains unclear and, thus, was examined in the current study. METHODS: In a crossover design outpatient study, 12 adults aged 24-36 years took 15 mg/kg/day (CA) or no **bile acid** supplement (control) while being fed a controlled diet (AHA **heart** -healthy diet). A liquid meal of defined composition was given on day 14 of the diet, and lumenal samples were collected. Thereafter, cholesterol absorption and cholesterol fractional synthetic rate (FSR) were assessed by stable isotopic methods from days 16 to 20. RESULTS: With CA **treatment**, bile was enriched significantly with CA ($P < 0.0004$) to 60.2% +/- 2.4% (mean +/- SEM) compared with 43.3% +/- 2.4% for controls. CA plus diet **treatment** significantly increased ($P = 0.013$) cholesterol absorption (72.6% +/- 2.9%) compared with diet **treatment** alone (60.4% +/- 2.9%). Percentage micellar cholesterol was increased by CA plus diet **treatment** vs. diet alone after meal ingestion ($P = 0.004$). Plasma total and high-density lipoprotein (HDL) and LDL cholesterol was unchanged with CA **treatment.**

CONCLUSIONS: Thus, enrichment in lumenal bile with CA results in an increase in cholesterol absorption, an effect potentially mediated by enhanced cholesterol solubilization in micelles.

L28 ANSWER 4 OF 19 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

2003314727 EMBASE Activation of muscarinic receptor signaling by **bile acids**: Physiological and medical implications. Raufman J.-P.; Cheng K.; Zimniak P.. Dr. J.-P. Raufman, Div. of Gastroenterol./Hepatology, Univ. of Maryland School of Medicine, 22 South Greene Street, Baltimore, MD 21201-1595, United States. Digestive Diseases and Sciences Vol. 48, No. 8, pp. 1431-1444 1 Aug 2003.
Refs: 118.
ISSN: 0163-2116. CODEN: DDSCDJ
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20030821

AB Besides their known physiological actions, **bile acids** are signaling molecules that alter cell function by interacting with muscarinic and nuclear receptors. **Bile acid** interaction with nuclear receptors modulates **bile acid** and cholesterol metabolism, whereas the potential consequences of muscarinic receptor activation are much broader. This review examines recent discoveries regarding **bile acid** interaction with muscarinic receptors. Selective and functional **bile acid** interaction has been reported with M3 receptors expressed in guinea pig gastric chief cells, human colon cancer cells, and transfected Chinese hamster ovary cells. Interaction of **bile acids** with chief cells may contribute to mucosal damage and other pathophysiological consequences of bile reflux. **Bile acid**-induced stimulation of muscarinic receptors on colon cancer cells may contribute to cellular proliferation and neoplasia. Potential consequences of **bile acid** interaction with muscarinic receptors on gastrointestinal myocytes, biliary epithelium, vascular endothelium and dermal neurons are discussed. Elucidation of molecular mechanisms underlying interaction of **bile acids** with muscarinic receptors may suggest new **treatments** for conditions that result from such interactions.

L28 ANSWER 5 OF 19 MEDLINE on STN DUPLICATE 2

2003174484. PubMed ID: 12620498. Inhibitory effects of ursodeoxycholic acid on the induction of nitric oxide synthase in vascular smooth muscle cells. Ma Ji; Nakajima Toshiaki; Iida Haruko; Iwasawa Kuniaki; Terasawa Kuniko; Oonuma Hitoshi; Jo Taisuke; Morita Toshihiro; Imuta Hiroyuki; Suzuki Jun ichi; Hirose Ken; Okuda Yukichi; Yamada Nobuhiko; Nagai Ryozo; Omata Masao. (Department of Cardiovascular, Respiratory Medicine and Gastroenterology, University of Tokyo, Graduate School of Medicine, 7-3-1 Hongo, Bunkyo, Japan.) European journal of pharmacology, (2003 Mar 19) 464 (2-3) 79-86. Journal code: 1254354. ISSN: 0014-2999. Pub. country: Netherlands. Language: English.

AB The expression of inducible nitric oxide synthase (iNOS) and the resultant increased nitric oxide production are associated with endotoxemia and atherosclerotic lesions observed in transplant **hearts** or balloon-injured artery. Ursodeoxycholic acid has been shown to have cardiovascular protective effects, such as inhibition of the development of transplant arteriosclerosis, but its mechanism remains unclear. Here, we investigated the effects of ursodeoxycholic acid on nitric oxide production and the expression of iNOS in vascular smooth muscle cells isolated from adult rat aorta and rabbit coronary artery. Nitrite released from cells in the culture medium was measured with the Griess reaction. iNOS mRNA and protein were measured by Northern and Western blot analyses. **Treatment** with ursodeoxycholic acid (30-1000 microM) significantly inhibited lipopolysaccharide plus interferon-gamma-induced nitric oxide production in a concentration-dependent manner, but ursodeoxycholic acid showed only small inhibitory effects on nitric oxide production that had already been induced by lipopolysaccharide plus

interferon-gamma. Ursodeoxycholic acid by itself did not affect basal nitric oxide production. Ursodeoxycholic acid also suppressed lipopolysaccharide plus interferon-gamma-induced expression of iNOS mRNA and protein. Ursodeoxycholic acid had the most potent inhibitory effect among various kinds of **bile acids** examined, i.e. chenodeoxycholic acid, deoxycholic acid, **cholic acid** and conjugated **bile acids** such as tauroursodeoxycholic acid. These results suggest that ursodeoxycholic acid inhibits the induction of iNOS and then nitric oxide production in aortic and coronary artery smooth muscle cells, suggesting a possible mechanism for the cardiovascular protective effect of ursodeoxycholic acid under various pathophysiological conditions such as endotoxemia and atherosclerosis.

L28 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
2002:107825 Document No. 136:156529 Molecularly imprinted polymers for the **treatment** and diagnosis of medical conditions. Green, Bernard S.; Priwler, Morris (Semorex, Inc., Israel). U.S. Pat. Appl. Publ. US 2002015690 A1 20020207, 15 pp. (English). CODEN: USXXCO. APPLICATION: US 2001-893643 20010629. PRIORITY: US 2000-2000/PV215882 20000630.
AB Improved molecularly imprinted polymers (MIPs) with both higher and more specific binding capacity for particular **bile acids** and/or salts, including the synthesis of such MIPs, the compds. themselves, and their specific applications are described. As an example of a particularly preferred specific application of these compds., the present invention encompasses the use of the MIPs as sequestrants in the gastrointestinal tract, particularly in order to bind and therefore remove toxins from the gastrointestinal tract. In addition, the present invention is also useful for **treatment** of various diseases which are related to, and/or characterized by, an effect of **bile acids** and salts, such as atherosclerosis, liver disease and various diseases of the gastrointestinal tract, e.g., gastroesophageal reflux disease and esophageal cancer. The MIP compds. of the present invention are also useful for combination therapy with other medications, such as ursodeoxycholic acid and antibodies against **bile acids** or salts, and for diagnosis and monitoring of diseases.

L28 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
2001:816498 Document No. 135:354777 Use of **bile acid** derivatives conjugated with metal ion chelated complexes for the diagnostic assessment of microvascular permeability. Cavagna, Friedrich; Roberts, Timothy P. L. (Bracco Imaging S.p.A., Italy; The Regents of the University of California). PCT Int. Appl. WO 2001082974 A2 20011108, 26 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP4324 20010417. PRIORITY: IT 2000-MI899 20000421.
AB The use of contrast agents of mol. weight lower than 5000 Dalton and including at least one residue of a biliary acid for the preparation of diagnostic contrast compns. for the microvascular permeability assessment is disclosed. An example is presented on MRI assessment of microvascular hyperpermeability in a rat breast tumor model using B-22956/1 as contrast agent and anti-VEGF **treatment.**

L28 ANSWER 8 OF 19 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
2001:469512 The Genuine Article (R) Number: 437QN. Low in vivo toxicity of a novel cisplatin-ursodeoxycholic derivative (Bamet-UD2) with enhanced cytostatic activity versus liver tumors. Dominguez M F; Macias R I R; Izco-Basurko I; De La Fuente A; Pascual M J; Criado J M; Monte M J; Yajeya J; Marin J J G (Reprint). Univ Salamanca, Dept Fisiol & Farmacol, Campus

Miguel Unamuno, ED S-09, Salamanca 37007, Spain (Reprint); Univ Salamanca, Dept Fisiol & Farmacol, Salamanca 37007, Spain. JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS (JUN 2001) Vol. 297, No. 3, pp. 1106-1112. ISSN: 0022-3565. Publisher: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cisplatin-**bile acid** derivatives belonging to the Bamet-family maintain both liver organotropism and cytostatic activity. "In vivo" toxicity and usefulness as chemotherapeutic agent versus liver tumors of a novel drug, Bamet-UD2 [cis-diamminechlorocholylglycinate platinum (II)], with enhanced "in vitro" cytostatic activity was investigated. Using orthotopically implanted mouse Hepa 1-6 hepatoma in the liver of Nude mice, the antitumor effect of Bamet-UD2 was compared with that of a previously characterized compound of this family, Bamet-R2 [cis-diamminebis-ursodeoxycholate platinum(II)], and cisplatin. Life span was significantly prolonged in mice treated with both Bamets (Bamet-UD2 > Bamet-R2), compared with animals receiving saline or cisplatin. All these drugs inhibit tumor growth (Bamet-UD2 = cisplatin > Bamet-R2), However, toxicity-related deaths only occurred under cisplatin **treatment.** Using rats maintained in metabolic cages, organ-specific toxicity and drug accumulation in tissues were investigated. The amount of both Bamets in the liver was severalfold higher than that of cisplatin, By contrast, a significantly higher amount of cisplatin in kidney and nerve was found. In lung, **heart**, muscle, brain, and bone marrow the amount of drug was small and also significantly lower in animals receiving Bamets. Signs of neurotoxicity (altered nerve conduction velocity), nephrotoxicity (increased serum urea and creatinine concentrations and decreased creatinine clearance), and bone marrow toxicity (decreased platelet and white blood counts) in animals treated with cisplatin but not with the Bamets were found. These results indicate that, owing to strong antitumor activity together with absence of side effects, Bamet-UD2 may be useful in the **treatment** of liver tumors.

L28 ANSWER 9 OF 19 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1999:746516 The Genuine Article (R) Number: 243DD. A pilot study on the hemodynamic effect of short-term ursodeoxycholic acid therapy in patients with stable liver cirrhosis. Baruch Y; Assy N; Weisbruch F; Reisner S A; Rinkevich D; Enat R; Blendis M; Bomzon A (Reprint). Technion Israel Inst Technol, Bruce Rappaport Fac Med, Dept Pharmacol, POB 9649, IL-31096 Haifa, Israel (Reprint); Technion Israel Inst Technol, Bruce Rappaport Fac Med, Dept Pharmacol, IL-31096 Haifa, Israel; Technion Israel Inst Technol, Bruce Rappaport Fac Med, Dept Med, IL-31096 Haifa, Israel; Technion Israel Inst Technol, Bruce Rappaport Fac Med, Dept Cardiol, IL-31096 Haifa, Israel; Rambam Med Ctr, Dept Med Band Cardiol, Liver Unit, Haifa, Israel; Ichilov Hosp, Dept Gastroenterol, IL-64239 Tel Aviv, Israel; Univ Calgary, Fac Med, Dept Med, Calgary, AB, Canada. AMERICAN JOURNAL OF GASTROENTEROLOGY (OCT 1999) Vol. 94, No. 10, pp. 3000-3004. ISSN: 0002-9270. Publisher: ELSEVIER SCIENCE INC, 655 AVENUE OF THE AMERICAS, NEW YORK, NY 10010 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB OBJECTIVE: Total serum **bile acid** concentrations are elevated in individuals with Liver disease. Ursodeoxycholic acid (UDCA) therapy in such patients results in a further significant rise in plasma levels to the extent that it becomes the major circulating **bile acid.** In laboratory animals, **bile acids**, such as taurocholic acid, have also been shown to possess a diuretic-like action, as they can promote diuresis, natriuresis, and kaliuresis by inhibiting tubular sodium reabsorption. The aim of the present study was to assess the effect of 1 month's UDCA therapy on cardiovascular function in cirrhotic patients.

METHODS: Two groups of patients with cirrhosis were studied, six with primary biliary cirrhosis (PBC) and six with postnecrotic liver cirrhosis (PNC). Cardiovascular function was assessed by determination of blood

pressure, **heart** rate, and by two-dimensional and pulsed Doppler echocardiography.

RESULTS: In PBC patients, 1 month's **treatment** with UDCA significantly reduced diastolic volume without changing systolic, diastolic, and mean blood pressures, **heart** rate, systolic and stroke volumes, ejection fraction, cardiac output, and systemic vascular resistance. In PNC patients, UDCA significantly reduced cardiac output, with a tendency to reduce left ventricular volumes, without any changes in systolic, diastolic, and mean blood pressures.

CONCLUSIONS: UDCA caused reductions in diastolic volume in the PBC patients and cardiac output in the PNC patients. Such reductions are not unlike that seen in individuals treated with diuretics. This diuretic-like action deserves further study, particularly in cirrhotic patients who are also being treated with diuretics or show evidence of cardiac myopathy. (C) 1999 by Am. Coll. of Gastroenterology.

L28 ANSWER 10 OF 19 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1998:690635 The Genuine Article (R) Number: 117ML. Plasma and hepatic cholesterol levels and fecal neutral sterol excretion are altered in hamsters fed straw mushroom diets. Cheung P C K (Reprint). Chinese Univ Hong Kong, Dept Biol, Shatin, New Territories, Hong Kong (Reprint). JOURNAL OF NUTRITION (SEP 1998) Vol. 128, No. 9, pp. 1512-1516. ISSN: 0022-3166. Publisher: AMER INST NUTRITION, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The effect of the fruiting body and mycelium of Volvariella volvacea (straw mushroom) on the concentrations of plasma lipids, liver cholesterol, fecal neutral sterol and **bile acid** excretions was investigated in male Golden Syrian hamsters. The hamsters were fed a purified hypercholesterolemic diet (0.1% cholesterol, 10% fat) for 4 wk to elevate plasma lipid concentrations. Twelve hamsters with elevated plasma total cholesterol were randomly assigned to each **treatment** group: control (5% cellulose), mushroom fruiting body (5%) and mushroom mycelium (5%). After 4 wk of mushroom diet consumption, the plasma total cholesterol, HDL cholesterol, and combined VLDL + LDL cholesterol concentrations (mmol/L) were significantly lower than control in the group fed the fruiting body-diet (40, 38 and 43%, respectively) ($P < 0.05$). The liver cholesterol levels were significantly lower in both the mushroom fruiting body- and the mycelium-fed groups (28 and 21% in terms of concentration; 39 and 30% in terms of total content, respectively) ($P < 0.05$) than that in the control group. Fecal neutral sterol excretion in the mushroom fruiting body- and mycelium-fed groups was significantly higher (81 and 74%, respectively) ($P < 0.05$) than that in the control group. Although no significant differences ($P > 0.05$) in the excretion of fecal **bile acids** were observed among groups fed the mushroom diets and the control diet, the mushroom fruiting body diet-fed hamsters apparently had less bacterial degradation of **cholic acid** as indicated by a significantly greater proportion ($P < 0.05$) of fecal **cholic acid** than in controls. They also had a significantly lower proportion of fecal deoxycholic acid (P (0.05). This study suggests that the fruiting body of the straw mushroom lowers elevated plasma cholesterol in hypercholesterolemic hamsters, whereas the mycelium does not.

L28 ANSWER 11 OF 19 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

97270503 EMBASE Document No.: 1997270503. Effect of dobutamine on serum **bile acid** levels in patients with cirrhosis. Konno T.; Tada K.; Akamatsu K.. Dr. K. Tada, Third Department Internal Medicine, Ehime University School of Medicine, Shitsukawa, Shigenobu, Onsen-gun, Ehime 791-02, Japan. Current Therapeutic Research - Clinical and Experimental Vol. 58, No. 8, pp. 515-524 1997.
Refs: 31.
ISSN: 0011-393X. CODEN: CTCEA

Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 970925
AB To investigate whether improving hepatic blood flow is effective as a **treatment** for cirrhosis we measured cardiac output and hepatic blood flow in eight patients with cirrhosis and hepatocellular carcinoma (5 women and 3 men, aged 51 to 64 years) who were given dobutamine intravenously through a peripheral vein. The relationship between changes in hepatic blood flow and changes in total **bile acid** concentration in the peripheral blood were assessed. Hepatic blood now was measured by using the xenon 133 gas clearance method with a catheter positioned in the portal vein. Dobutamine infusion increased cardiac output and hepatic blood flow to 133.9% and 111.4% of preinfusion values, respectively, and decreased total serum **bile acid** concentration 120 minutes after the start of infusion to 59.0% of the pretreatment value. The **bile acids**, in descending order of the highest percent decrease, were ursodeoxycholic, cholic, deoxycholic, chenodeoxycholic, and lithocholic; however, there were no significant differences between the free, glycine-conjugated, and taurine-conjugated forms. The percent decrease in total serum **bile acids** was significantly correlated with the percent increase in hepatic blood flow. These findings suggest that increasing blood flow could be an effective way to decrease total serum **bile acid** levels and thus possibly promote liver function in patients with cirrhosis.

L28 ANSWER 12 OF 19 MEDLINE on STN DUPLICATE 3
96314245. PubMed ID: 8724029. Cyclosporin A-mediated cholestasis in patients with chronic hepatitis after **heart** transplantation.
Myara A; Cadranel J F; Dorent R; Lunel F; Bouvier E; Gerhardt M; Bernard B; Ghoussoub J J; Cabrol A; Gandjbakhch I; Opolon P; Trivin F. (Department of Biochimie, Hopital Saint-Joseph, Paris, France.) European journal of gastroenterology & hepatology, (1996 Mar) 8 (3) 267-71. Journal code: 9000874. ISSN: 0954-691X. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Viral chronic hepatitis often occurs in **heart** transplant recipients receiving cyclosporin. This essential immunosuppressive drug may induce cholestasis. We investigated the effect of **treatment** with cyclosporin on serum conjugated **bile acids** in patients with chronic hepatitis developing after **heart** transplantation. Fifty-nine patients were studied: 17 with chronic hepatitis, 15 **heart** transplant patients with normal alanine aminotransferase activity, and 27 **heart** transplant patients with chronic hepatitis, the last two groups receiving cyclosporin. Hepatic biochemical tests and total **bile acid** concentration were determined on fasting blood samples. The individual glyco- and tauroconjugated **bile acids** were quantified by high-performance liquid chromatography and direct spectrometry. In patients taking cyclosporin the bilirubin concentration and the alkaline phosphatase activity were increased only when hepatitis was present, in association with a slight increase in **cholic acid** level (5.13 microM vs. 0.68 microM; $P < 0.01$). Conjugated lithocholate concentration was dramatically higher when hepatitis and immunosuppression with cyclosporin were associated (1.17 microM vs. 0.03 and 0.04 microM; $P < 0.01$). Chenodeoxycholate was the main circulating **bile acid** only in the **heart** transplant patients treated with cyclosporin but without hepatitis. These results suggest that the mechanisms which explain the cyclosporin-associated modifications of the **bile acid** pool are different according to the presence or absence of hepatitis. The occurrence of hepatitis in patients on cyclosporin led to an increase in serum lithocholate and primary **bile acid** concentrations. Further studies are required to assess the effect of ursodeoxycholic acid for this cholestasis.

L28 ANSWER 13 OF 19 MEDLINE on STN DUPLICATE 4
96033638. PubMed ID: 7482380. [**Bile acids** in liver

diseases--current indications]. Gallensauren bei Lebererkrankungen--neue Indikationen. Stiehl A. (Medizinische Universitatsklinik, Heidelberg.) Therapeutische Umschau. Revue therapeutique, (1995 Oct) 52 (10) 682-6. Ref: 29. Journal code: 0407224. ISSN: 0040-5930. Pub. country: Switzerland. Language: German.

AB Ursodeoxycholic acid (UDCA) has beneficial effects in cholestatic diseases such as primary biliary cirrhosis, primary sclerosing cholangitis and cholestasis of pregnancy. In chronic hepatitis and alcoholic hepatitis, an effect of UDCA is uncertain. After organ transplantation (liver, bone, **heart**), favorable effects of UDCA which await confirmation were observed. UDCA very likely has a beneficial effect in children with Byler's and Alagille's syndrome, extrahepatic biliary atresia after the Kasai procedure and in cholestasis of cystic fibrosis. Unclear is the effect of UDCA in benign intermittent cholestasis (Summerskill-Tygstrup syndrome). Children with cholestasis and inborn errors of **bile acid** synthesis need additional administration of a primary **bile acid** (**cholic acid**, chenodeoxycholic acid). UDCA **treatment** in general does not lead to definitive cure of the disease but to improvement of laboratory parameters and possibly of symptoms and liver histology, and liver transplantation may be postponed to a later time point.

L28 ANSWER 14 OF 19 MEDLINE on STN DUPLICATE 5

89193474. PubMed ID: 2930479. Processing of cholesteryl ester from low-density lipoproteins in the rat. Hepatic metabolism and biliary secretion after uptake by different hepatic cell types. Kuipers F; Nagelkerke J F; Bakkeren H; Havinga R; Van Berkel T J; Vonk R J. (Department of Pediatrics, University of Groningen, The Netherlands.) Biochemical journal, (1989 Feb 1) 257 (3) 699-704. Journal code: 2984726R. ISSN: 0264-6021. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Biliary secretion of the cholesteryl ester moiety of (modified) low-density lipoprotein (LDL) was examined under various experimental conditions in the rat. Human LDL or acetylated LDL (acetyl-LDL), radiolabelled with [3H]cholesteryl oleate, was administered intravenously to unanesthetized rats equipped with permanent catheters in the bile duct, duodenum and **heart**. LDL was cleared relatively slowly from plasma, mainly by Kupffer cells. At 3 h after injection, only 0.9% of the radioactivity was found in bile; after 12 h this value was 4.5%. Uptake of LDL by hepatocytes was stimulated by **treatment** of the rats with 17 alpha-ethinyloestradiol (EE; 5 mg/kg for 3 successive days); this resulted in a more rapid secretion of radioactivity into bile, 3.9% and 12.4% after 3 h and 12 h respectively. The extremely rapid uptake of acetyl-LDL via the scavenger pathway, mainly by endothelial cells, resulted in the secretion of only 2.1% of its 3H label into bile within 3 h, and 9.5% within 12 h. Radioactivity in bile was predominantly in the form of **bile acids**; only a small part was secreted as free cholesterol. However, the specific radioactivity of biliary cholesterol was higher than that of **bile acids** in all three experimental conditions. EE-treated animals did not form **cholic acid** from [3H]cholesteryl oleate, which was a major product of the cholesteryl oleate from LDL and acetyl-LDL in untreated rats, but formed predominantly very polar **bile acids**, i.e. muricholic acids. It is concluded that uptake of human LDL or acetyl-LDL by the liver of untreated rats is not efficiently coupled to biliary secretion of cholesterol (**bile acids**). This might be due to the anatomical localization of their principal uptake sites, the Kupffer cells and the endothelial cells respectively. Induction of LDL uptake by hepatocytes by EE **treatment** warrants a more efficient disposition of cholesterol from the body via bile.

L28 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

1988:35279 Document No. 108:35279 Modulation of low density lipoprotein receptor activity by **bile acids**: differential effects of chenodeoxycholic and ursodeoxycholic acids in the hamster. Malavolti,

Mauro; Fromm, Hans; Ceryak, Susan; Roberts, Ingram M. (Med. Cent., George Washington Univ., Washington, DC, 20037, USA). Journal of Lipid Research, 28(11), 1281-95 (English) 1987. CODEN: JLPRAW. ISSN: 0022-2275.

AB Hamsters were fed chenodeoxycholic acid (CDC), ursodeoxycholic acid (UDC), or no **bile acid.** [14C]sucrose-labeled hamster low-d. lipoprotein (LDL) and methylated human LDL were infused i.v. to study LDL receptor-dependent and LDL receptor-independent organ uptake, resp., of LDL. Biliary CDC increased during both CDC and UDC **treatment.** The UDC enrichment of bile after UDC feeding was relatively small. **Bile acid** synthesis was suppressed after both **bile acid treatments.** Under the condition of an acute bile fistula, the hamster LDL uptake increased in the liver, **heart**, and adrenals in the CDC-treated animals. During an intact enterohepatic circulation, the hepatic uptake of hamster LDL, which accounted for a major portion of the total uptake, was increased after UDC **treatment.** The hamster LDL uptake in the colon, which represented only a small fraction of the total uptake, increased after CDC **treatment.** When hamster LDL was infused at increasing concns., its uptake was significantly higher in the UDC-treated than in the control and CDC-treated animals. The methylated human LDL uptake showed no significant changes in the different **treatment** groups under either exptl. condition. The study shows significantly different effects of CDC and UDC on LDL receptor activity. Since these differences are expressed in spite of a similar suppression of **bile acid** synthesis, UDC may directly influence LDL receptor activity.

L28 ANSWER 16 OF 19 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

1981:158109 Document No.: PREV198171028101; BA71:28101. COMPARISON OF THE EFFECTS BETWEEN URSO DEOXY **CHOLIC-ACID** AND CHENO DEOXY **CHOLIC-ACID** ON LIVER FUNCTION AND STRUCTURE AND **BILE ACID** COMPOSITION IN THE RHESUS MONKEY MACACA-MULATTA. SARVA R P [Reprint author]; FROMM H; FARIVAR S; SEMBRAT R F; MENDELOW H; SHINOZUKA H; WOLFSON S K. MONTEFIORE HOSP, 3459 FIFTH AVE, PITTSBURGH, PA 15213, USA. Gastroenterology, (1980) Vol. 79, No. 4, pp. 629-636.
CODEN: GASTAB. ISSN: 0016-5085. Language: ENGLISH.

AB The hepatotoxic potential of the cholelitholytic **bile acids**, chenodeoxycholic (chenic) and ursodeoxycholic acids, was compared in the rhesus monkey [M. mulatta.] A placebo-controlled **treatment** trial with 40 and 120 mg/kg per day doses of chenic acid and ursodeoxycholic acid, respectively, was conducted in 20 animals. Chenic and ursodeoxycholic acids induced comparable abnormalities of liver function and structure. Liver biopsies, performed before and after 6 mo. of **treatment**, showed the development of distinct light microscopic changes, including inflammation, fibrosis and ductular proliferation in the portal fields as well as lobular rearrangement with formation of septa and regenerative nodules. EM confirmed light microscopy, but showed no specific changes of cell organelles. Light microscopic examination of the kidneys, lungs, **heart**, intestine and brain in 10 monkeys, which were sacrificed after 6 mo. of controlled **bile acid treatment**, showed no abnormalities. Biliary lithocholic acid, all of which was unsulfated, increased several-fold to comparable levels in the **bile acid** -treated groups. Follow-up studies 6 mo. after termination of **bile acid treatment** showed normalization of liver function tests and of **bile acid** composition as well as a considerable improvement of the histologic abnormalities. The restitution of normal liver structure was incomplete, with fibrosis and mild inflammation persisting in the portal fields. In this primate species, chenic and ursodeoxycholic acids apparently have comparable hepatotoxic effects, which are associated with similar increases of unsulfated lithocholic acid in bile. [Chenodeoxycholic (chenic) acid and its 7β-epimer, ursodeoxycholic acid, are presently being studied for their efficacy and safety in the dissolution of cholesterol gallstones in

humans.].

L28 ANSWER 17 OF 19 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN DUPLICATE 6
81015895 EMBASE Document No.: 1981015895. The effects of cholates on smooth muscle strips and cardiac muscle. Ro J.Y.; Cho T.S.; Hong S.S.. Dept. Pharmacol., Yonsei Univ. Coll. Med., Seoul, Korea, Republic of. Korean Journal of Pharmacology Vol. 16, No. 1, pp. 41-50 1980.
CODEN: TYCPAQ
Pub. Country: Korea, Republic of. Language: Korean. Summary Language: English.
ED Entered STN: 911209
AB Chenodeoxycholic acid (CDCA) has been used as a gallstone dissolving agent since 1972. Recently, ursodeoxycholic acid (UDCA) has been reported to be effective in dissolving gallstones. Both **bile acids** increased bile flow. The increase in bile flow associated with an increase in cholesterol level in bile after CDCA or UDCA infusion was reported. In this study, using the smooth muscle strips of guinea pig and fowl, responses of the cholates were observed. In addition, the influence of adrenergic blocking agents on the response of the strips to cholates was investigated. Also the effects of cholates on cardiac function were examined by using isolated atria of rabbit and **heart** of anesthetized frog. The results were as follows: All cholates, such as UDCA, CDCA, and CA produced a marked inhibitory effect on the motility in isolated duodenal strip of guinea pig and fowl; however, only UDCA showed the contraction in the isolated esophagus of fowl. These effects of cholates were blocked by propranolol. In isolated guinea pig stomach strip and gall bladder, cholates exhibited a marked inhibitory effect on the motility and the effects due to UDCA and CA were blocked by phenoxybenzamine while CDCA was not affected. The spontaneous and ouabain-induced arrhythmia was partially abolished by cholates. However, concomitant administration of cholates with ouabain or epinephrine caused a marked prolongation in occurrence of atrial arrhythmia in comparison with ouabain or epinephrine alone in isolated rabbit atria. In the **heart** of anesthetized frog, the epinephrine-induced arrhythmia was partially abolished by cholates. The combined **treatment** with cholates and ouabain or epinephrine produced a marked prolongation in occurrence of the arrhythmia in comparison with ouabain or epinephrine alone. From these results, it can be suggested that the effects of cholates on the smooth muscle of duodenum and esophagus are produced in response to adrenergic β-receptor and the effect on gall bladder and stomach is more likely due to the direct effect on the muscle. In addition, cholates exhibit a slight antiarrhythmic effect on **heart**, therefore, cholates can be classified as a nonselective antiarrhythmic drug, such as propranolol.

L28 ANSWER 18 OF 19 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
79119538 EMBASE Document No.: 1979119538. Arylsulfonate esters of fatty alcohols: IV. Effects on cholesterol catabolism. Klauda H.C.; Bell F.P.; Grogan W.M.; Quackenbush F.W.. Dept. Biochem., Purdue Univ., West Lafayette, Ind. 47907, United States. Lipids Vol. 13, No. 10, pp. 627-635 1978.
CODEN: LPDSAP
Pub. Country: United States. Language: English.
AB Hypercholesterolemic rats, fed 1% cholesterol and 0.5% glycocholate, were treated with arylsulfonates in various ways to observe the pattern of cholesterol elimination. Dietary linoleyl p-toluene-sulfonate (LTS) hastened return to normocholesterolemia and lowered hepatic cholesterol either with or without continued cholesterol feeding. LTS administered via the portal vein significantly lowered plasma cholesterol in 48 hr; ethyl linoleate and monoolein produced no lowering. LTS administered via the portal vein to glycocholate-infused rats increased the biliary excretions of label from [4-14C] cholesterol administered intracardially and also increased total **bile acid** excretion 21%

without increased bile volume when compared to similar injection of ethyl linoleate. No change in biliary excretion of cholesterol was seen. **Bile acid** kinetics were studied by using isotopic dilution techniques. Cholate turnover was enhanced by feeding oleyl p-toluenesulfonate (OTS) and oleyl p-(n-decyl)benzenesulfonate (ODS) as suggested by a 16-35% decrease in half-life in both normal and hypercholesterolemic rats. Rats consuming a grain-based colony diet had a 54% increase in cholate synthesis when OTS was included in the diet. The composition of bile was changed when either OTS or ODS was fed; an increase in chenodeoxycholate was noted. This change was gradual with OTS but rapid with ODS and paralleled enhanced decay of chenodeoxycholate specific radioactivity in response to **treatment.** ODS and OTS also increased 184CO2 expiration from oral [26-14C] cholesterol in hypercholesterolemic rats. Dietary OTS and ODS elevated hepatic free cholesterol in hypercholesterolemic rats; ODS also elevated plasma free cholesterol and increased cholesteryl ester hydrolase activity in the liver. The data suggest that arylsulfonates stimulate cholesterol catabolism, in addition to the reported inhibition of cholesterol absorption.

L28 ANSWER 19 OF 19 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

74070168 EMBASE Document No.: 1974070168. Turnover of **bile acids** in the hypercholesterolemic rat as influenced by saturation of dietary fat. McGovern R.F.; Quackenbush F.W.. Dept. Biochem., Purdue Univ., West Lafayette, Ind. 47907, United States. Lipids Vol. 8, No. 8, pp. 466-469 1973.
CODEN: LPDSAP
Language: English.

AB Injections of [24-14C] chenodeoxy cholate and 3H cholate were made by **heart** puncture into 300 g male rats that bore T cannulas in their bile ducts. The animals had been raised on diet A, containing glucose, cholesterol and cholate, or diet B, containing sucrose and cholesterol; each of the diets contained 5% safflower oil or 5% beef tallow as variables. From analysis of bile samples collected from the T at intervals over a 5 day period, it was observed that the safflower oil group fed diet B had a 17% shorter cholate half life, a 29% larger cholate pool size and 52% higher rate of cholate synthesis than those fed beef tallow in the same diet. The safflower group fed diet A also had a larger cholate pool size, but synthesis and half life were obscured by cholate feeding. Chenodeoxy cholate turnover data were not obtainable because the decay curves were bimodal for all **treatments** and hence did not conform to a simple pool model. It is concluded that dietary safflower oil causes more rapid formation of cholate than does dietary beef tallow in the cholesterol fed rat.

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=> s (anker s?/au or coats a?/au or volk h?/au or schumann r?/au)
L29       7094 (ANKER S?/AU OR COATS A?/AU OR VOLK H?/AU OR SCHUMANN R?/AU)

=> s l29 and bile acid
L30          5 L29 AND BILE ACID

=> dup remove l30
PROCESSING COMPLETED FOR L30
L31          5 DUP REMOVE L30 (0 DUPLICATES REMOVED)

=> d l31 1-5 cbib abs

L31  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2005 ACS on STN
2000:645885  Document No. 133:217694  Endotoxin-modulating compounds for
     therapy of heart failure and cachexia.  Anker, Stefan;
     Coats, Andrew; Volk, Hans-Dieter; Rauchhaus, Mathias;
     Schumann, Ralf Reiner (Max-Delbruck-Centrum fur Molekulare
     Medizin, Germany).  PCT Int. Appl. WO 2000053224 A2 20000914, 74 pp.
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DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2299 20000309.
PRIORITY: GB 1999-5300 19990309; GB 1999-5307 19990309; GB 1999-5310 19990309; GB 1999-5314 19990309; GB 1999-5315 19990309.

AB A method of treating, preventing or ameliorating chronic or acute heart failure in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, **bile acids**, or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a **bile acid** or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. A method of treating, preventing or ameliorating endotoxin-mediated immune activation in acute or chronic heart failure in a patient comprises administering to the patient an effective amount of a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, **bile acids** or an antibody capable of binding LPS, a compound that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a **bile acid** or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. Also disclosed is a method for treating cachexia and wasting syndromes due to diseases other than congestive heart failure.

L31 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
2000:645835 Document No. 133:217707 Therapy of cachexia and wasting syndromes with **bile acids**. **Anker, Stefan**; **Coats, Andrew**; **Volk, Hans-dieter**; **Schumann, Ralf Reiner**; Plauth, Mathias; Lochs, Herbert (Max-Delbruck-Centrum fur Molekulare Medizin, Germany). PCT Int. Appl. WO 2000053165 A2 20000914, 26 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2062 20000309.
PRIORITY: GB 1999-5315 19990309; GB 1999-5300 19990309; GB 1999-5310 19990309; GB 1999-5307 19990309; GB 1999-5314 19990309.

AB The present invention relates to therapy and the use of agents in the therapy of cachexia and wasting syndromes due to diseases other than congestive heart failure. Cachexia occurs in a number of other chronic diseases, like liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, and rheumatoid arthritis. Cachexia and weight loss are linked to inflammatory processes and they are linked to increased mortality and/or morbidity. Cytokine activation is a potential causal mechanism for the development of cachexia also in these other diseases. The invention describes a method of treating or ameliorating body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis in a patient. The method comprises administering to the patient

an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS). The invention describes also a method of treating, preventing or ameliorating endotoxin-mediated immune activation in body wasting or cachexia in a patient with liver cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis. The method comprises administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS). The ability of ursodeoxycholic acid and BPI protein to inhibit LPD-mediated NFT production in the whole blood of patients with cachexia is shown.

L31 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
1937:26097 Document No. 31:26097 Original Reference No. 31:3634e-f
Bile acids and their practical application in medicine.
Kunze, H.; **Volk, H.** Muenchener Medizinische Wochenschrift, 82, 869-71 (Unavailable) 1935. CODEN: MMWOAU. ISSN: 0027-2973.
AB Three prepns. consisting of cholic acid derivs. combined with garlic oil are described.

L31 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
1923:4093 Document No. 17:4093 Original Reference No. 17:730c-i Unsaturated **bile acids.** III. Relations of apocholic acid, dihydroxycholenic acid (m. 260°) and cholic acid to desoxycholic acid. Boedecker, F.; **Volk, H.** Ber., 55B, 2302-9 (Unavailable) 1922.
AB cf. C. A. 16, 1217. It had been found that cholic acid (A) with dehydrating agents yields chiefly 2 unsatd. acids, C24H38O4, apocholic (B) and di-hydroxycholenic (C), m. 260°. B, like desoxycholic acid (D), forms with many organic substances addition products analogous to the choleic acids (E). It was concluded that B is closely related to D and that probably the two HO groups occupy the same positions in both acids, although no direct proof of this, by hydrogenation of B, could be obtained. Further study of B has now shown that on degradation with Br it gives about 40% of a dihydroxycholadienic acid (F), which can no longer form E-like addition products and takes up 1 Mol. H2 to form an acid identical in all respects except optical activity with B, whence the non-hydrogenizable double bond of F must be identical with the double bond in B. Since C forms no E-like addition products and it differs considerably in chemical and phys. properties from B it had been concluded that in is formation another HO group than that in the formation of B is involved in the dehydration, but this assumption has been found to be incorrect. If C is degraded with Br like B it gives F in even better yield (at least 60%), whence there can be no doubt that B and C are formed by elimination of the same HO group from A and that they differ only in the positions of the unsatd. unions. C easily takes up 1 mol. H2 and yields D quant. Both HO groups in B and C therefore occupy the same positions as those in D; at the same time this is the first direct proof that two HO groups of A are identical with those of D and hence that A passes into D by elimination of 1 mol. of H2O and addition of one of H2. Seeing that the hydrogenation product of C is identical, even optically, with natural D, it is probable that in the formation of C from A no asym. C atom of the D is involved, and that the double bond of C lies between 2 sec. C atoms. F, obtained in 14-6 g. yield from 30 g. AcOH-B in 250 cc. McOH at-10° slowly treated with 3.6 cc. Br in 50 cc, MeOH, poured into ice water, which ppts. a soft yellow tar, kneaded until it falls to a powder, filtered, washed, dried and saponified with alc. KOH, m. 245-7°, decolorizes alkaline KMnO4 and Br in MeOH, [α]D1823.0° (absolute alc.). The alkali salts are soluble in H2O and alc.; the Mg and Ba salts are precipitated from not too dilute solns. of the alkali salts as oils, which become crystalline on boiling; silver salt, fine needles; methyl ester, from the acid with CH2N2, sinters 79°, m. 85°.

L31 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

1922:7145 Document No. 16:7145 Original Reference No. 16:1217a-d The unsaturated **bile acids.** II. An isomer of apocholic acid. Bodecker, Fr.; **Volk, H.** Ber., 54B, 2489-92 (Unavailable) 1921.

AB cf. C. A. 15, 858. It was shown in the earlier work that cholic acid on treatment with dehydrating agents yields a mixture of unsatd. **bile acids** from which the difficultly soluble apocholic acid (A) can be isolated easily and in good yield by means of Et2O. In the residue difficultly soluble in alc., which was then believed to be unchanged cholic acid, there has now been found an acid isomeric with A, isolated by alternate crystallization from AcOH and alc. and obtained pure only through the Me ester. It seps. from EtOH-H2O in long fine woolly needles, m. 259-60°, immediately decolorizes KMnO4 in cold Na2CO3, quickly decolorizes Br in MeOH suspension at 0°, is tasteless, gives the Pettenkofer reaction, [α]D27 57.3° (alc.), forms alkali salts easily soluble in alc. and H2O; the magnesium salt seps. as an oil, which changes into fine needles on boiling; the calcium and barium salts are likewise amorphous in the cold, the latter changing into felted needles with 6H2O on heating. Methyl ester, from the Ag salt with MeI, stout prisms with 1 MeOH, which it loses only at a high temperature, m. 85-90°, [α]D25 60.27° (MeOH), mol. weight in boiling MeOH 442. The new acid is apparently not a secondary rearrangement product of A for it cannot be obtained from A with AcOH-ZnCl2 or dilute H2SO4; in its formation another HO group than in the formation of A is evidently involved in the dehydration.

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=> s l29 and endotoxin
L32         322 L29 AND ENDOTOXIN

=> s l32 and heart failure
L33         118 L32 AND HEART FAILURE

=> s l33 and treatment
L34          22 L33 AND TREATMENT

=> dup remove l34
PROCESSING COMPLETED FOR L34
L35            8 DUP REMOVE L34 (14 DUPLICATES REMOVED)

=> d l35 1-8 cbib abs

L35 ANSWER 1 OF 8  EMBASE  COPYRIGHT (c) 2005 Elsevier B.V. All rights
    reserved on STN
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2005137145 EMBASE Future prospects of anticytokine therapy in chronic **heart failure.** von Haehling S.; **Anker S.D.**.
Dr. S. von Haehling, Imperial Coll. School of Medicine, Department of Clinical Cardiology, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, United Kingdom. stephan.von.haehling@web.de. Expert Opinion on Investigational Drugs Vol. 14, No. 2, pp. 163-176 2005.
Refs: 108.
ISSN: 1354-3784. CODEN: EOIDER
Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20050414

AB Several lines of evidence suggest that chronic **heart failure** is a state of chronic inflammation. Indeed, various pro-inflammatory markers, including the cytokines TNF-α, and interleukin 6 and 1, are activated in the course of the disease. In chronic **heart failure**, these substances are frequently induced even before the classical neurohormones angiotensin II and noradrenaline. Although the recently published anti-TNF-α trials with etanercept and infliximab have called the beneficial effects of targeting single cytokines into question, the overactive immune system

remains a promising target for therapeutic interventions, which aim at slowing down disease progression. Broader approaches are required. These comprise targeting bacterial lipopolysaccharide (**endotoxin**) that enters the circulation through the oedematous gut wall, immune modulation therapy with patient-derived whole blood exposed to oxidative stress, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (the so-called statins) and a number of other substances including pentoxifylline and thalidomide. .COPYRGT. 2005 Ashley Publications Ltd.

L35 ANSWER 2 OF 8 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2004:401340 The Genuine Article (R) Number: 819GK. Procalcitonin-guided antibiotic **treatment** in **heart failure.**
Sandek A; Springer J; Habedank D; Brunkhorst F; **Anker S D (Reprint).** Dept Cardiol, Div Appl Cachexia Res, Charite Campus Virchow Klinikum, Augustenburger Pl, D-13353 Berlin, Germany (Reprint); Dept Cardiol, Div Appl Cachexia Res, D-13353 Berlin, Germany. LANCET (8 MAY 2004) Vol. 363, No. 9420, pp. 1555-1555. ISSN: 0140-6736. Publisher: LANCET LTD, 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND. Language: English.

L35 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 1

2004283437. PubMed ID: 15182775. Selective intestinal decontamination in advanced chronic **heart failure**: a pilot trial.
Conraads Viviane M; Jorens Philippe G; De Clerck Luc S; Van Saene Hendrik K; Ieven Margaretha M; Bosmans Johan M; Schuerwegh Annemie; Bridts Chris H; Wuyts Floris; Stevens Wim J; **Anker Stefan D**; Rauchhaus Mathias; Vrints Christiaan J. (Department of Cardiology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium.. Viviane.Conraads@uza.be) . European journal of heart failure : journal of the Working Group on Heart Failure of the European Society of Cardiology, (2004 Jun) 6 (4) 483-91. Journal code: 100887595. ISSN: 1388-9842. Pub. country: Netherlands. Language: English.

AB BACKGROUND AND AIMS: **Endotoxin**, derived from intestinal aerobic Gram-negative bacilli (AGNB), could be an important monocyte activator in chronic **heart failure** (CHF). The effect of selective decontamination of the digestive tract (SDD) on intracellular monocyte cytokine production, monocyte CD14 expression, circulating **endotoxin** and cytokines, and flow-mediated dilation (FMD) was studied in patients with severe CHF. METHODS AND RESULTS: Ten patients with CHF (NYHA class III-IV) were enrolled in a non-placebo controlled pilot trial involving the administration of SDD (polymyxin B, tobramycin) for 8 weeks. One patient was later excluded due to cardiac transplantation. Before **treatment**, after 4 and 8 weeks therapy, and 6 weeks post-**treatment**, monocyte CD14 expression, intracellular monocyte production of interleukin-1beta [IL-1beta], interleukin-6 [IL-6], tumour necrosis factor (TNF)-alpha with and without lipopolysaccharide (LPS) stimulation were measured. Concentrations of **endotoxin** and cytokines (IL-1beta, IL-6, TNF-alpha) were also determined. AGNB in faeces, intestinal **endotoxin** and FMD were assessed at baseline, after 4 weeks of **treatment** and 6 weeks post-**treatment.** SDD eradicated intestinal AGNB (P<0.00001) and decreased faecal **endotoxin** concentrations (P<0.00001). There was a significant decline in monocyte CD14 expression (P=0.03) and in IL-1beta (P=0.0001), IL-6 (P=0.02) and TNF-alpha (P=0.0002) production after 4 and 8 weeks of **treatment** in the basal state and for IL-1beta (P=0.008) and IL-6 (P=0.005) after LPS stimulation. FMD significantly improved at 4 weeks and returned to baseline after **treatment** discontinuation (P=0.002). Circulating concentrations of **endotoxin** and cytokines remained unchanged. CONCLUSION: Reduction of the intestinal **endotoxin** pool led to a decrease in monocyte CD14 expression and intracellular cytokine production in patients with severe CHF. The improvement of peripheral endothelial function could be a marker of the anti-inflammatory effect of SDD.

L35 ANSWER 4 OF 8 MEDLINE on STN DUPLICATE 2

2005139950. PubMed ID: 15772704. Statins: a **treatment** option for chronic **heart failure**?. Haehling Stephan von; Okonko Darlington O; **Anker Stefan D.** (National Heart and Lung Institute, Department of Clinical Cardiology, Imperial College School of Medicine, London, UK, and Division of Applied Cachexia Research, Department of Cardiology, Charite Medical School, Berlin, Germany.) Heart failure monitor, (2004) 4 (3) 90-7. Journal code: 101140283. ISSN: 1470-8590. Pub. country: England: United Kingdom. Language: English.

AB Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, consistently reduce cardiovascular risk. It has recently emerged that cholesterol reduction is not their only mode of action, with current research largely focused on the pleiotropic effects of statins. These include the improvement of endothelial dysfunction, their anti-inflammatory properties, and the mobilization of bone marrow-derived endothelial progenitor cells. All these effects are potentially beneficial in chronic **heart failure** (CHF), although prospective trials are needed to confirm this. However, cholesterol reduction by statins per se may prove detrimental in patients with CHF, as cholesterol seems to be able to inactivate **endotoxin** as a stimulus for proinflammatory cytokine production. It is therefore tempting to speculate that low doses of statins still confer pleiotropic effects without lowering plasma cholesterol levels.

L35 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 3

2003529563. PubMed ID: 14607199. Invasive assessment of bacterial **endotoxin** and inflammatory cytokines in patients with acute **heart failure.** Peschel Thomas; Schonauer Martin; Thiele Holger; **Anker Stefan D**; Schuler Gerhard; Niebauer Josef. (Herzzentrum der Universitat Leipzig, Strumpellstrasse 39, 04289 Leipzig, Germany.) European journal of heart failure : journal of the Working Group on Heart Failure of the European Society of Cardiology, (2003 Oct) 5 (5) 609-14. Journal code: 100887595. ISSN: 1388-9842. Pub. country: Netherlands. Language: English.

AB AIMS: To test the hypothesis that during acute **heart failure endotoxin** might be increased in hepatic veins as a sign of bacterial or **endotoxin** translocation from the bowel into the blood stream. METHODS AND RESULTS: In patients with acute **heart failure** (NYHA IV; n=17) levels of **endotoxin**, soluble (s) CD14, tumor necrosis factor alpha (TNFalpha and interleukin 6 (IL6)) were measured in blood drawn from an antecubital vein on admission and compared with age-matched patients with stable chronic **heart failure** (n=21) and healthy volunteers (n=9). All levels were systemically elevated during acute **heart failure** (all P<0.05); once patients were stable enough to undergo cardiac catheterization, **endotoxin** was found to be significantly higher in hepatic veins (0.62+/-0.05 EU/ml) than left ventricles (0.46+/-0.04 EU/ml; P<0.05), whereas sCD14, TNFalpha and IL6 were not different between these sites. At follow-up (29+/-6 days) **endotoxin** but not sCD14, TNFalpha or IL-6 was significantly lower as compared to baseline (P<0.05). CONCLUSIONS: Higher levels of **endotoxin** in hepatic veins as compared to the left ventricle during acute **heart failure** are suggestive of bacterial or **endotoxin** translocation from the bowel into the blood stream. This may lead to new **treatment** strategies. The lack of difference in TNFalpha levels between the pulmonary artery and the left ventricle sheds doubt on the heart as a source of systemically elevated TNFalpha levels.

L35 ANSWER 6 OF 8 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

2002294975 EMBASE Effect of interleukin-10 on the production of tumor necrosis factor-alpha by peripheral blood mononuclear cells from patients with chronic **heart failure.** Bolger A.P.; Sharma R.; Von Haehling S.; Doehner W.; Oliver B.; Rauchhaus M.; **Coats A.J.S.** ; Adcock I.M.; **Anker S.D.**. A.P. Bolger, Department of Clinical

Cardiology, National Heart and Lung Institute, London SW3 6LY, United Kingdom. a.bolger@ic.ac.uk. American Journal of Cardiology Vol. 90, No. 4, pp. 384-389 15 Aug 2002.
Refs: 29.
ISSN: 0002-9149. CODEN: AJCDAG
S 0002-9149(02)02494-3. Pub. Country: United States. Language: English.
Summary Language: English.
ED Entered STN: 20020829
AB Chronic **heart failure** (HF) is a state of inflammatory immune activation characterized by elevated circulating levels of tumor necrosis factor-α (TNF-α). Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that inhibits TNF-α production and lessens **endotoxin** bioactivity. It is not known whether IL-10 reduces lipopolysaccharide (LPS) stimulated TNF-α production of peripheral blood mononuclear cells (PBMCs) from patients with chronic HF. PBMCs were isolated from 15 patients with chronic HF (New York Heart Association functional class 3.0 ± 0.2, left ventricular ejection fraction 30 ± 2%, peak oxygen consumption 18.1 ± 0.8 ml/kg/min) and 15 healthy control subjects and stimulated with 1 and 10 ng/ml LPS for 24 hours with or without prior addition of IL-10 (10 ng/ml). TNF-α was quantified in cell-free supernatants by an enzyme-linked immunosorbent assay. TNF-α, soluble TNF receptors, IL-10, and LPS were quantified in plasma. LPS stimulated TNF-α production was highest in those patients in New York Heart Association class II ($p < 0.01$ vs New York Heart Association class III and IV, $p < 0.001$ vs control subjects). IL-10 reduced PBMC TNF-α production in all stimulated samples at 1 and 10 ng/ml LPS (mean reduction 43% at 1 ng/ml, $p < 0.01$ and 55% at 10 ng/ml, $p < 0.0001$). The percentage reduction in TNF-α release did not differ significantly between patients and control subjects or with respect to severity of chronic HF or baseline immune parameters. Independently of clinical severity, IL-10 profoundly inhibits TNF-α release from PBMCs isolated from patients with chronic HF. IL-10 is, therefore, a potential therapy for use in chronic HF associated with inflammatory immune activation. .COPYRGT. 2002 by Excerpta Medica, Inc.

L35 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 4
2000486462. PubMed ID: 11036910. The **endotoxin**-lipoprotein hypothesis. Rauchhaus M; **Coats A J**; **Anker S D.**
(Department of Clinical Cardiology, National Heart and Lung Institute, London, UK.. m.rauchhaus@ic.ac.uk) . Lancet, (2000 Sep 9) 356 (9233) 930-3. Ref: 31. Journal code: 2985213R. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The advent of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) has revolutionised the **treatment** of hypercholesterolaemia. Statin **treatment**, by lowering the atherogenic lipoprotein profile, reduces morbidity and mortality in patients with cardiovascular disease. **Treatment** with simvastatin causes a reduction of events of new-onset **heart failure**, but this may be attributable to properties other than its lipid-lowering effects. There is some evidence that lower serum cholesterol concentrations (as a surrogate for the totality of lipoproteins) relate to impaired survival in patients with chronic **heart failure** (CHF). Inflammation is a feature in patients with CHF and increased lipopolysaccharide may contribute substantially. We postulate that higher concentrations of total cholesterol are beneficial in these patients. This is potentially attributable to the property of lipoproteins to bind lipopolysaccharide, thereby preventing its detrimental effects. We hypothesise there is an optimum lipoprotein concentration below which lipid reduction would, on balance, be detrimental. We also propose that, in patients with CHF, a non-lipid-lowering statin (with ancillary properties such as immune modulatory and anti-inflammatory actions) could be as effective or even more beneficial than a lipid-lowering statin.

L35 ANSWER 8 OF 8 MEDLINE on STN DUPLICATE 5

1999285942. PubMed ID: 10359409. **Endotoxin** and immune activation in chronic **heart failure**: a prospective cohort study.
Niebauer J; **Volk H D**; Kemp M; Dominguez M; **Schumann R R**; Rauchhaus M; Poole-Wilson P A; **Coats A J**; **Anker S D.**
(Cardiac Medicine, National Heart and Lung Institute, Imperial College School of Medicine, London, UK.) Lancet, (1999 May 29) 353 (9167) 1838-42. Journal code: 2985213R. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: Immune activation in patients with chronic **heart failure** may be secondary to **endotoxin** (lipopolysaccharide) action. We investigated the hypothesis that altered gut permeability with bacterial translocation and endotoxaemia would be increased in patients with oedema secondary to congestive **heart failure.** METHODS: We compared 20 patients who had chronic **heart failure** with recent-onset peripheral oedema (mean age 64 years [SD 10], New York Heart Association [NYHA] class 3.3 [0.7]), 20 stable non-oedematous patients with chronic **heart failure** (mean age 63 years [19], NYHA class 2.6 [0.7]), and 14 healthy volunteers (mean age 55 years [16]). Biochemical markers of endotoxaemia, inflammation, and immune activation were measured. Ten patients were studied within 1 week of complete resolution of oedema. Five patients survived longer than 6 months and were restudied again after remaining free of oedema for more than 3 months. FINDINGS: Mean **endotoxin** concentrations were higher in oedematous patients with chronic **heart failure** than in stable patients with chronic **heart failure** (0.74 [SD 0.45] vs 0.37 EU/mL [0.23], p=0.0009) and controls (0.46 EU/mL [0.21], p=0.02). Oedematous patients had the highest concentrations of several cytokines. After short-term diuretic **treatment, endotoxin** concentrations decreased from 0.84 EU/mL [0.49] to 0.45 EU/mL [0.21], p<0.05) but cytokines remained raised. After freedom of oedema for more than 3 months after oedema resolved, **endotoxin** concentrations remained unchanged from the previous visit (0.49 EU/mL [0.06], p=0.45). INTERPRETATION: Raised concentrations of **endotoxin** and cytokines are found in patients with chronic **heart failure** during acute oedematous exacerbation. Intensified diuretic **treatment** can normalise **endotoxin** concentrations. Our preliminary findings suggest that **endotoxin** may trigger immune activation in patients with chronic **heart failure** during oedematous episodes.

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=> s urodesoxycholic acid
L36             4 URODESOXYCHOLIC ACID

=> s l36 and cachexia
L37             0 L36 AND CACHEXIA

=> s l36 and liver cirrhosis
L38             0 L36 AND LIVER CIRRHOSIS

=> s liver cirrhosis
L39        134409 LIVER CIRRHOSIS

=> s l39 and cachexia
L40           117 L39 AND CACHEXIA

=> s l40 and bile acid
L41             3 L40 AND BILE ACID

=> dup remove l41
PROCESSING COMPLETED FOR L41
L42             3 DUP REMOVE L41 (0 DUPLICATES REMOVED)

=> d l42 1-3 cbib abs
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L42 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
2005:136529 Document No. 142:212406 Method for treating **cachexia** with RXR retinoid ligands. Jiang, Guang Liang; Yuan, Yang-Dar; Chandraratna, Roshantha A. (Allergan, Inc., USA). PCT Int. Appl. WO 2005013949 A2 20050217, 173 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US25564 20040806. PRIORITY: US 2003-PV493138 20030807; US 2003-PV533734 20031231.

AB The invention discloses a method for the treatment of **cachexia** in a subject in need of treatment. More specifically, the invention discloses the use of retinoid compds. that act on retinoid X receptors (RXRs) for the treatment of **cachexia** in a subject in need of treatment. The **cachexia** is associated with a complication of a primary disease, condition or disorder. Primary diseases, conditions and disorders include, but are not limited to, cancer, AIDS, **liver cirrhosis**, diabetes mellitus, chronic renal failure, chronic obstructive pulmonary disease, chronic cardiac failure, immune system diseases (e.g., rheumatoid arthritis and systemic lupus erythematosus), tuberculosis, cystic fibrosis, gastrointestinal disorders (e.g., irritable bowel syndrome and inflammatory bowel disease), Parkinson's disease, anorexia nervosa, dementia, major depression, an aged condition, and sarcopenia.

L42 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
2000:645835 Document No. 133:217707 Therapy of **cachexia** and wasting syndromes with **bile acids.** Anker, Stefan; Coats, Andrew; Volk, Hans-dieter; Schumann, Ralf Reiner; Plauth, Mathias; Lochs, Herbert (Max-Delbruck-Centrum fur Molekulare Medizin, Germany). PCT Int. Appl. WO 2000053165 A2 20000914, 26 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP2062 20000309. PRIORITY: GB 1999-5315 19990309; GB 1999-5300 19990309; GB 1999-5310 19990309; GB 1999-5307 19990309; GB 1999-5314 19990309.

AB The present invention relates to therapy and the use of agents in the therapy of **cachexia** and wasting syndromes due to diseases other than congestive heart failure. **Cachexia** occurs in a number of other chronic diseases, like **liver cirrhosis**, chronic obstructive pulmonary disease, chronic renal failure, diabetes, and rheumatoid arthritis. **Cachexia** and weight loss are linked to inflammatory processes and they are linked to increased mortality and/or morbidity. Cytokine activation is a potential causal mechanism for the development of **cachexia** also in these other diseases. The invention describes a method of treating or ameliorating body wasting or **cachexia** in a patient with **liver cirrhosis**, chronic obstructive pulmonary disease, chronic renal failure, diabetes, rheumatoid arthritis in a patient. The method comprises administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS). The invention describes also a method of treating, preventing or ameliorating endotoxin-mediated immune activation in body wasting or **cachexia** in a patient with **liver cirrhosis**, chronic obstructive pulmonary disease, chronic renal failure, diabetes,

rheumatoid arthritis. The method comprises administering to the patient an effective amount of a compound that is able to reduce the production, absorption and/or the effect of an endotoxin (lipopolysaccharide; LPS). The ability of ursodeoxycholic acid and BPI protein to inhibit LPD-mediated NFT production in the whole blood of patients with **cachexia** is shown.

L42 ANSWER 3 OF 3 MEDLINE on STN

96265478. PubMed ID: 8672739. Influence of clinicopathological variables on CYP protein expression in human liver. George J; Byth K; Farrell G C. (Department of Gastroenterology and Hepatology, University of Sydney at Westmead Hospital, New South Wales, Australia.) Journal of gastroenterology and hepatology, (1996 Jan) 11 (1) 33-9. Journal code: 8607909. ISSN: 0815-9319. Pub. country: Australia. Language: English.

AB Drug metabolism is usually impaired in malnourished patients with decompensated cirrhosis, but the separate influence of clinicopathological variables, including nutritional status, on the expression of hepatic cytochrome P450 proteins has not been well characterized. We determined the hepatic content of CYP1A2, CYP2C8/10, CYP2E1 and CYP3A proteins in 71 subjects, 21 with histologically normal livers and 50 with chronic liver disease, and then tested for potential relationships between patient variables and individual CYP proteins by multivariate linear regression analysis. Variables analysed included nutritional status (determined by experienced clinicians), serum albumin and bilirubin concentrations, prothrombin time, the grade of ascites and hepatic encephalopathy, and the Child-Pugh score. Impaired nutrition and **cachexia** were associated with reductions of CYP2C8/10 levels of approximately 19 and 39%, respectively, relative to cases in which nutrition was replete. Similarly, CYP2E1 protein was reduced by approximately 13 and 26%, according to the apparent severity of nutritional impairment. In contrast, nutritional status did not contribute to variability in expression of CYP1A2 or CYP3A proteins. Of the clinicopathological variables analysed, only serum bilirubin was shown to have an independent influence on CYP protein content. Thus, elevated serum bilirubin concentrations were associated with significant declines in the contents of CYP1A2 and CYP2C8/10 but not CYP3A or CYP2E1. The mechanisms for the effects of nutritional status and serum bilirubin concentration on the levels of CYP proteins are unclear, but could be mediated by factors such as cytokines, dietary composition and alterations in the level of serum **bile acids.** Knowledge of the influence of clinicopathological factors and nutritional status on CYP expression should lead to more rational drug prescribing in patients with hepatic disease.

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---Logging off of STN---

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Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	339.46	339.67

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-19.71	-19.71